Randomised trial of three doses of inhaled nitric oxide in acute respiratory distress syndrome

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Abstract

Background—Inhaled nitric oxide (iNO) is a potential therapeutic agent for the management of acute respiratory distress syndrome (ARDS). Concerns remain, however, regarding the potential toxicity from iNO and/or its oxidative derivatives and methaemoglobinaemia.

Aims—To determine the risk of toxicity from iNO, which includes worsening of lung injury, a prospective study evaluating the acute effects of three concentrations of iNO on gas exchange and haemodynamics in 12 children with ARDS was performed in a tertiary paediatric intensive care unit.

Intervention—iNO was administered for one hour at three concentrations (1, 10, and 20 parts per million (ppm)) in a random order of possible dosing schedules to avoid dose accumulation bias. Arterial blood gas, methaemoglobin concentrations, and haemodynamic parameters were obtained at baseline before commencement of iNO, at the end of each study hour, and after iNO was discontinued. Nitric oxide and nitrogen dioxide concentrations were continuously monitored during the study.

Results—iNO significantly improved the oxygenation ratio (P_{aO_2}/F_{iO_2}) from a mean (SEM) baseline of 11.9 (1.7) kPa to 20 (3.9) kPa, 24 (4.5) kPa, and 21.6 (3.9) kPa at 1, 10, and 20 ppm iNO, respectively. There was no significant difference in the improvement in oxygenation achieved between the three concentrations. Correspondingly, there was a significant improvement in oxygenation index (pre-iNO 28.3 (5) *v* post-iNO 18 (3) (1 ppm), 15 (3) (10 ppm), 16 (3) (20 ppm)). No toxicity from methaemoglobinaemia or nitrogen dioxide was seen during iNO administration.

Conclusion—The results show that a low concentration of iNO (1 ppm) is as effective as higher concentrations (10 and 20 ppm) in improving oxygenation in children with ARDS and may be important in minimising toxicity during iNO use.

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Acute respiratory distress syndrome (ARDS) represents the severe end of the spectrum of acute lung injury.¹ Although the initiating events are numerous, the major pathophysiological feature of ARDS is cardiorespiratory

dysfunction, characterised by pulmonary hypertension, intrapulmonary shunting with severe hypoxaemia, and myocardial dysfunction.²

Over the years, advances have been made in the understanding of ARDS pathophysiology and in the therapeutic approaches to ventilatory management of this difficult intensive care problem. Despite this, the mortality in both adults and children remains high. In children, mortality related to acute respiratory distress syndrome is in excess of 50% in some published series.³⁻⁴

Conventional intensive care management has included mechanical ventilation, inotropic support, and intravenous vasodilators.⁵ However, with progressive respiratory failure, the aggressive ventilator management that may be necessary to maintain gas exchange can lead to secondary lung injury, presumably from over-distension and oxygen toxicity. Furthermore, currently available intravenous vasodilators lack specificity for the pulmonary vascular bed and may further worsen intrapulmonary shunting by causing non-selective vasodilation of pulmonary arteries that perfuse underventilated lung regions.⁶

The discoveries during the last decade defining endogenous nitric oxide (NO) as an endothelium derived relaxing factor⁷ have led to the development of inhaled NO (iNO) as a clinical tool, including a potential therapeutic role in the management of ARDS. The mechanism of action of iNO in ARDS is not fully understood but includes selective reduction of pulmonary vascular resistance (PVR) and improved ventilation-perfusion matching.^{8,9}

The main concern with iNO use, especially in children, is potential toxicity related to the formation of oxidative derivatives of NO, which may further worsen the lung injury^{10,11} as well as causing methaemoglobinaemia. Furthermore, paradoxically, very high concentrations of iNO may worsen ventilation-perfusion matching by diffusing across the lung and enhancing the perfusion of non-ventilated lung regions.¹²

It is difficult to establish an optimal dose regimen, but the aim should be to use as low an effective dose as possible, thus minimising the risks of potential toxicity. There are few data on iNO dosage for paediatric ARDS; two previous published manuscripts have used 20 parts per million (ppm),¹³ and 11 and 60 ppm¹⁴ iNO. In this prospective study, we compare the acute blood gas and haemodynamic effects of 1, 10, and 20 ppm iNO, administered in a random order, in children with ARDS. Our hypothesis is that low dose iNO (1 ppm) is as efficacious in

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Table 1 Patient characteristics

Patient	Age (months)	Associated diagnosis	Lung injury score	Duration of iNO (hours)	Duration of intubation (days)	Outcome
1	135	<i>Staphylococcus aureus</i> sepsis and MOF	3	44	15	Survived
2	15	Crush injury with pulmonary contusion, liver haematoma, and spleen laceration	3	59	11	Survived
3	5	Smoke inhalation	3	45	11	Survived
4	48	Sepsis postbone marrow transplant for stage IV neuroblastoma	4	202	19	Died
5	52	Immersion injury	4	12	7	Survived
6	17	Pneumonia	4	141	52	Survived
7	139	ARDS secondary to GCSF (in child with Crohn's disease)	4	184	27	Survived
8	6	Sepsis with MOF	3	168	5	Died
9	10	Ex-premature, CLD, postsurgery for recurrent diaphragmatic hernia	3	189	38	Survived
10	3	RSV bronchiolitis	4	130	27	Survived
11	5	<i>Streptococcus pneumoniae</i> sepsis and RSV bronchiolitis	4	63	3	Died
12	36	Severe head injury	4	33	2	Died

MOF, multiorgan failure; GCSF, granulocyte colony stimulating factor; CLD, chronic lung disease; RSV, respiratory syncytial virus.

improving oxygenation as higher doses (10 and 20 ppm).

Methods

This study was approved by the ethics committee of the Royal Alexandra Hospital for Children, Sydney, New South Wales, Australia. Written parental consent was obtained in all cases and the use of iNO as an investigational product had been approved by the Therapeutic Goods Administration, Canberra, Australia.

STUDY POPULATION

The first 12 consecutive patients with ARDS (table 1) admitted to the hospital's paediatric intensive care unit were enrolled. The median age was 16 months (range 3–139 months). The diagnosis of ARDS was as defined by the American-European Consensus Conference of ARDS.¹

STUDY PROTOCOL

The haemodynamic and blood gas effects of three concentrations of inhaled nitric oxide (1, 10, and 20 ppm) were studied. Each patient acted as his or her own control. The three concentrations were administered in a random order, as opposed to a stepwise increment in concentrations, such that dose accumulation bias was avoided and the ordering of doses was balanced for the study overall. Each concentration was administered for one hour. Arterial blood gases and methaemoglobin levels (ABL System 625, Radiometer, Copenhagen, Denmark) were measured before the commencement of iNO, and at the end of each study hour. The ventilator settings remained unchanged during the study duration. At the end of the last study dose, iNO was discontinued and baseline measurements were, where possible, repeated after one hour (measurements were made earlier if there was a pronounced deterioration in oxygen saturation). Reinstitution of iNO and the subsequent continued use of iNO was at the discretion of the clinical team.

All patients studied were given muscle relaxants, sedated, and ventilated with either the Babylog 8000 (Dräger, Australia) (seven patients), or Servo 300 (Siemens, Sweden) (five

patients). The choice of ventilator was in accordance with established ventilation protocols in the unit and was dependent on weight (less than 10 kg, Babylog 8000; more than 10 kg, Servo 300). A pressure limited, permissive hypercapnia ventilation strategy, aiming for tidal volumes of 5–10 ml/kg with 5–10 cm H₂O of positive end expiratory pressure, was used in all patients. Nitric oxide (1000 ppm, BOC, Australia) was delivered either via a combined nitric oxide delivery and analysis unit, (NODOMO, Dräger, Germany), when using the Babylog 8000, or by a continuous flow of NO into the inspiratory limb of the ventilator circuit, when using the Servo 300.¹⁵ Both systems allowed continuous monitoring of NO and nitrogen dioxide (NO₂) concentrations. All expired gases were scavenged.

For all patients, heart rate, systemic arterial pressures, and peripheral oxygen saturation were continuously monitored (Omnicare Component Monitoring System, Hewlett Packard, Australia). Right heart and pulmonary artery catheterisation is not routine in our institution and was not performed in any of our patients.

Serial oxygenation, ventilation, and haemodynamic parameters were expressed as group mean (SEM) derived from individual raw data, and these mean data were then compared using repeated measures analysis of variance. Significant results were inferred at $p < 0.05$.

Results

Twelve patients were studied using this protocol. It was a heterogeneous group of patients and the most common cause of acute lung injury was infection ($n = 6$), either systemic sepsis or a pulmonary infection. All patients had severe lung injury with acute lung injury scores greater than 2.5 (table 1). Before commencement of iNO, the mean P_{aO_2}/F_{iO_2} was 11.9 (1.7) kPa, the mean oxygenation index was 28 (5) (oxygenation index = $P_{aw} \times F_{iO_2}/P_{aO_2} \times 100\%$; P_{aw} = mean airway pressure, P_{aO_2} = postductal arterial partial pressure of oxygen, F_{iO_2} = inspired oxygen fraction), and the mean ventilation index was 44 (6) (ventilation index = peak inspiratory

Table 2 Summary of changes (mean (SEM)) in P_{aO_2}/F_{iO_2} , oxygenation index, ventilation index, and mean systemic arterial pressure with inhaled nitric oxide for all patients

	Baseline	1 ppm	10 ppm	20 ppm	On discontinuation of iNO
P_{aO_2}/F_{iO_2} (kPa)	11.9 (1.7)	20 (3.9)*	24 (4.5)*	21.6 (3.9)*	14.3 (2.5)
OI	28.3 (5)	18 (3)*	15 (3)*	16 (3)*	24 (4)
VI	43.8 (6.3)	39.1 (5.0)	39.1 (5.2)	38.9 (5.3)	42.1 (7.5)
mSAP	60 (2)	63 (4)	65 (4)	67 (3)	61 (4)

OI, oxygenation index; VI, ventilation index; mSAP, mean systemic arterial pressure. * $p < 0.05$.

pressure $\times$ rate $\times$ $P_{aCO_2}/1000$; P_{aCO_2} = partial pressure of carbon dioxide).

Overall, the mean P_{aO_2}/F_{iO_2} improved from a baseline of 11.9 (1.7) kPa to 20 (3.9) kPa, 24 (4.5) kPa, and 21.6 (3.9) kPa at 1, 10, and 20 ppm iNO, respectively ($p = 0.0002$) (table 2). The overall mean percentage improvement in P_{aO_2}/F_{iO_2} from baseline was 80 (27)%, 107 (36)%, and 102 (33)% at the three concentrations, respectively. There was, however, no significant difference in improvements in the oxygenation ratio achieved between the three concentrations.

Using an arbitrary level of 20% as significant clinical improvement in oxygenation ratio, response was seen in oxygenation in 11 patients during the administration of iNO at any dose. One child (patient 1) did not show any improvement at any of the three concentrations, another child (patient 4) only had an improvement in oxygenation at iNO concentrations of 10 and 20 ppm, while a third child (patient 9) only had a 20% improvement in P_{aO_2}/F_{iO_2} after inhalation of 10 ppm NO (fig 1).

Correspondingly, there was a significant improvement in oxygenation index (pre-iNO 28.3 (5) *v* post-iNO 18 (3) (at 1 ppm), 15 (3) (at 10 ppm), 16 (3) (at 20 ppm)) ($p = 0.0002$). There was no significant change in ventilation index during the intervals with and without iNO ($p = 0.98$). As no ventilator changes were made during the study, this indicates that iNO, although improving oxygenation, did not significantly alter P_{aCO_2} .

Figure 1 Changes in P_{aO_2}/F_{iO_2} with inhaled nitric oxide.

In 11 of the 12 patients, arterial blood gases were obtained after discontinuation of iNO. The mean P_{aO_2}/F_{iO_2} after discontinuation of iNO was 14.3 (2.5) kPa and was not significantly different from the baseline value ($p = 0.16$).

The mean systemic arterial pressure did not change significantly from baseline at any of the three concentrations (pre-iNO 60 (2) mmHg *v* 63 (4) mmHg (at 1 ppm), 65 (4) mmHg (at 10 ppm), and 67 (3) mmHg (at 20 ppm)) ($p = 0.1535$). Neither was there a significant change in the mean systemic arterial pressure when iNO was discontinued, compared to the initial baseline mean of 61 (4) mmHg ($p = 0.93$).

At the conclusion of this four hour study, the attending physician was permitted to continue iNO if a clinically significant improvement in oxygenation (more than 20%) had been achieved. As a result, in 10 patients, iNO was continued beyond the study protocol. In these patients, iNO was maintained at a low dose of 1 to 10 ppm (in accordance with our paediatric intensive care unit protocol at the time of this study). The duration of exposure in these patients ranged from 12 to 202 hours. The median duration of intubation in survivors was 21 days (range 7–52 days).

No toxicity was observed. Specifically, methaemoglobin measurements did not exceed 2.5% (seen in one child at 20 ppm iNO) and the maximum NO_2 concentration was 1 ppm.

There were four deaths in the group; three had an associated or underlying diagnosis of sepsis (patients 4, 8, and 11), and the fourth child (patient 12) had severe head injury with respiratory failure.

Discussion

It has been over five years since the initial reports of the clinical use of iNO in persistent pulmonary hypertension of the newborn.^{16,17} Progress in our understanding of its effects and use has occurred during this period, and iNO has been used therapeutically, as well as a diagnostic tool, in a variety of other conditions such as ARDS, pulmonary hypertension of congenital¹⁸ and acquired¹⁹ heart disease, primary pulmonary hypertension,²⁰ and chronic obstructive airways disease.²¹

Inhaled NO may be beneficial in the management of ARDS by reducing PVR and the consequent pulmonary oedema, and improving right and left ventricular function. Also, by improving ventilation-perfusion matching, iNO may improve gas exchange; this in turn may decrease the need for ventilator support, and thus reduce the risks of attendant ventilator induced lung injury and facilitate new ventilator strategies, including permissive hypercapnia and the use of low tidal volumes.²²

The mechanism of action of iNO in acute lung injury remains under investigation. Kavanagh and colleagues, in an oxidant induced lung injury model, have shown that iNO may attenuate increases in capillary permeability.²³ It has also been shown that iNO reduces not only the arterial component of PVR but also the venous component, thereby increasing the reabsorption rate of pulmonary

oedema.²⁴ Preliminary studies have shown that iNO modifies the inflammatory response of the lung²⁵ and iNO may reduce the hyperproduction of some cytokines in patients with severe ARDS.²⁶ In a porcine model of endotoxin shock, iNO was shown to reduce selectively pulmonary hypertension while improving arterial oxygenation and pH with a pronounced attenuation of sympathetic activation.²⁷

Despite the potential benefits of iNO in the management of ARDS, its potential toxicity makes it important to define a minimal effective concentration. The formation of peroxynitrite, hydroxyl radicals, and nitrogen dioxide could potentially inactivate surfactant, injure endothelial or type II alveolar cells, or amplify inflammation,¹³ thereby leading to further lung injury.

In adult studies, doses ranging from 0.01 to 100 ppm have been shown to improve oxygenation and/or pulmonary artery hypertension in ARDS. There is much less published data with regards to the use of iNO in children with ARDS. Using iNO at 20 ppm, Abman and colleagues showed an acute improvement in oxygenation and reduction in PVR, without adverse haemodynamic effects, in 10 children with ARDS.¹³ In a prospective, randomised study of 19 children aged seven months to 16 years, Day and colleagues showed that PVR and systemic oxygenation were acutely improved to a similar extent by 11 and 60 ppm iNO; they suggested that concentrations in excess of 10 ppm were probably not needed for prolonged therapy of children with severe lung disease.¹⁴

In this study, we have compared the effects of three doses of iNO at 1, 10, and 20 ppm in children with ARDS. Our results show that iNO improved oxygenation in children with ARDS, without a difference in the improvement in oxygenation achieved between the three doses used.

ARDS may follow diverse aetiological triggers. Despite a range of admitting diagnoses, all subjects in this study had evidence of uniformly severe lung involvement with lung injury scores²⁸ greater than 2.5 (table 1). However, because of the small numbers and diverse diagnostic groups, we did not feel justified in relating the individual NO response to severity of ARDS.

In this study, we have not attempted to identify an ideal dose, as this is difficult with the heterogeneity and variable response of the patients, shown here as well as by other authors. However, we have shown that iNO at 1 ppm is as efficacious as higher doses (10 or 20 ppm) in improving oxygenation in children with no obvious toxicity problems. This may prove significant in minimising potential toxicity as inhaled nitric oxide evolves a role as an adjunctive therapy in the intensive care management of children with ARDS.

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