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Early Administration of Inhaled Nitric Oxide to Children with Acute Respiratory Distress Syndrome and Its Effects on Oxygenation and Ventilator Settings: Prospective Preliminary Report of Ten Patients

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Aim. To establish a protocol for the early introduction of inhaled nitric oxide (iNO) therapy in children with acute respiratory distress syndrome (ARDS) and to assess its acute and sustained effects on oxygenation and ventilator settings.

Patients and Methods. Ten children with ARDS, aged 1 to 132 months (median, 11 months), with arterial saturation of oxygen < 88% while receiving a fraction of inspired oxygen (FiO_2) ≥0.6 and a positive end-expiratory pressure of ≥10 cm H_2O were included in the study. The acute response to iNO was assessed in a 4-hour dose-response test, and positive response was defined as an increase in the PaO_2/FiO_2 ratio of 10 mmHg above baseline values. Conventional therapy was not changed during the test. In the following days, patients who had shown positive response continued to receive the lowest iNO dose. Hemodynamics, PaO_2/FiO_2, oxygenation index, gas exchange, and methemoglobin levels were obtained when needed. Inhaled nitric oxide withdrawal followed predetermined rules.

Results. At the end of the 4-hour test, all the children showed significant improvement in the PaO_2/FiO_2 ratio (63.6%) and the oxygenation index (44.9%) compared with the baseline values. Prolonged treatment was associated with improvement in oxygenation, so that FiO_2 and peak inspiratory pressure could be quickly and significantly reduced. No toxicity from methemoglobin or nitrogen dioxide was observed.

Conclusion. Administration of iNO to children is safe. iNO causes rapid and sustained improvement in oxygenation without adverse effects. Ventilator settings can safely be reduced during iNO treatment.

Key words: *child welfare; methemoglobin; multiple organ failure; nitric oxide; respiratory distress syndrome; ventilation, mechanical*

Acute respiratory distress syndrome (ARDS) is the most severe manifestation of acute lung injury. It has been associated with high mortality rate, despite better understanding of its pathophysiology and recent therapeutic advances (1). There is an inflammatory process that causes disruption of the alveolar-capillary barrier with consequent interstitial and alveolar edema. The ventilation/perfusion ($\dot{V}/\dot{Q}$) mismatching and intrapulmonary shunting causes refractory hypoxemia, and a decrease in lung compliance can be present (2). There is also an increase in pulmonary vascular resistance, which has a quick onset and persists even after correction of hypoxia. The pulmonary vascular resistance level correlates with the severity of lung injury and mortality (3). Right ventricular failure and low cardiac output may be the consequences of pulmonary hypertension (4).

Treatment of underlying infections and ventilatory support are the major prerequisites for ARDS clinical management. Although arterial oxygenation may be effectively improved by mechanical ventilation, it does not reduce pulmonary hypertension. More aggressive ventilatory strategies using high tidal volume and peak inspiratory pressure (Pip) induce alveolar overdistention and cyclic reopening of collapsed alveoli, extending inflammatory structural injury to well-ventilated lung areas (5).

The pathophysiology of ARDS suggests that positive effects can be achieved with the therapeutic use of vasodilators. However, systemic vasodilator therapy has been limited by its inability to reduce pulmonary vascular resistance without adversely affecting systemic blood pressure. In addition, it can worsen gas exchange by increasing the perfusion of underventilated lung regions (6).

In the late 1980's, nitric oxide (NO) was identified as the endothelial-derived relaxing factor (7,8). Its physiological effects were first presented in 1992 (9,10). Because of its high affinity for hemoglobin, inhaled nitric oxide (iNO) is rapidly and very specifically inactivated in the blood (11) and does not vasodilate the systemic circulation. The rationale for its use in ARDS is that the iNO-induced vasodilation of pulmonary vasculature adjacent to well-ventilated al-

veoli increases blood flow to these lung areas and preferentially shunts blood away from poorly ventilated regions, matching $\dot{V}/\dot{Q}$ and reducing intrapulmonary shunt. This results in improved oxygenation and reduction of both pulmonary vascular resistance and right ventricular afterload (12). By improving $\dot{V}/\dot{Q}$ matching, iNO may allow less aggressive mechanical ventilation, which minimizes the risk of ventilator-induced lung injury and morbidity (13).

There is, however, little information about the appropriate time for iNO introduction, dosage, side effects, and weaning in children (14).

The aims of this prospective study performed in children with ARDS were 1) to establish a protocol for the early introduction of iNO associated with conventional therapy, 2) to determine the acute and sustained effects of iNO on some oxygenation indexes and ventilator settings, 3) to analyze the weaning process, and 4) to assess the safety of NO inhalation.

Patients and Methods

This study was approved by the Human Research and Ethics Committee of the University Hospital of Botucatu Medical School. Written informed consent was obtained from the parents or guardians of each child before enrollment.

Patients

Children with ARDS (15), aged between one month and 12 years and admitted to the Pediatric Intensive Care Unit (PICU) at Botucatu Medical School in 1999, were considered potential subjects for this study. Initial ventilatory management was performed with time-cycled pressure-limited ventilators. Positive end-expiratory pressure (Peep) was increased incrementally to recruit lung volume and maximize oxygenation, while avoiding clinical and radiographic signs of lung hyperinflation. Tidal volume and Pip were limited to <8 mL/kg and to ≤35 cm H_20, respectively, permitting hypercapnia if necessary and accepting arterial saturation of oxygen ($Sa0_2$) between 88% and 90%. The choice of ventilator was in accordance with the ventilation protocol established by the Pediatric Intensive Care Unit, depending on the children's weight (less than 10 kg: Sechrist IV-100B, Sechrist Industries; Anaheim, CA, USA; more than 10 kg: Inter 5, Intermed; São Paulo, Brazil). Eligibility of the patients required Peep of ≥10 cm H_2O to guarantee minimally "open" alveoli, the so-called "open lung approach" (16), and hemodynamic stability. Only the patients with $Sa0_2$ less than 88% despite the optimal ventilator settings and with a fraction of inspired oxygen ($Fi0_2$) ≥0.6 were immediately assigned to the treatment protocol.

Patients with congenital heart diseases and chronic lung diseases were excluded. The inclusion and exclusion criteria are summarized in Table 1.

Routine procedure of ARDS management included treatment of the underlying diseases and sedation, with continuous intravenous infusion of midazolam and/or fentanyl. The patients were paralyzed by the continuous intravenous infusion of atracurium when necessary. Optionally, prone positioning was used as a part of conventional treatment (17). Hemodynamic support included the optimization of intravascular fluid volume, guided by central venous pressure monitoring and administration of catecholamines (dopamine, dobutamine, and norepinephrine).

The patients were monitored according to standard pediatric intensive care protocol. All the children had a radial artery catheter for continuous monitoring of systolic, diastolic, and mean arterial pressure, and for blood gas sampling. Arterial blood was drawn from indwelling catheter for measurement of PaO_2, $PaCO_2$, and SaO_2 as needed. Other biochemical values to calculate pediatric risk of mortality (PRISM) score and to assess coexisting multiple organ system failure were obtained from central venous line. Lung function status was assessed by the oxygenation index (OI = mean airway pressure × FiO_2 × 100/PaO_2; cm H_2O/mm Hg) and the PaO_2/FiO_2 ratio (mm Hg). The OI was used both as a measure of oxygenation and as an indicator of aggressiveness of mechanical ventilatory support. Methemoglobin concentration was measured immediately before and at each arterial blood gas analysis after the beginning of iNO therapy.

Diagnosis of multiple organ system failure was based on the criteria proposed by Wilkinson et al (18) and modified by Fioretto et al (19). Sepsis and septic shock were defined according to the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference (20). The PRISM (21) and lung injury score (22) were calculated for each patient at enrollment in the study.

Inhaled Nitric Oxide Administration

Inhaled nitric oxide administration followed the guidelines and techniques previously described (23-25). Briefly, NO blended with nitrogen was obtained from 20-L tanks connected to a pressure regulator (AGA Medical S.A., São Paulo, Brazil). The concentration in the tanks was certified by the suppliers as 300 parts per million (ppm) of nitric oxide in nitrogen. The NO was continuously delivered to the patients *via* flowmeter, directly into the inspiratory limb of the ventilator circuit, distal to humidifier from a point 30 cm distal to the child's tracheal tube. Inhaled nitric oxide and nitric dioxide (NO_2) concentrations were measured using an electrochemical sensor (JP Moryia Ind & Com Ltda, São Paulo, Brazil) from samples of circuit gas obtained as close as possible to the tracheal tube via Y-piece. The NO/NO_2 electrochemical sensor gas analyzer was calibrated before use every day. Audio-visual alarms were calibrated at a dose of 1 ppm above the iNO administered dose and at a maximum level of 3 ppm of NO_2 concentration. The delivery system was flushed thoroughly before use.

Study Design

The patients who reached entrance criteria were enrolled in the study within 1 h (Table 1). Baseline measurements (time zero; T0) were made at steady-state pressure control ventilation immediately before starting iNO administration. Inhaled NO was administered at a dose-response test of 20 ppm for 30 min under the previously mentioned ventilator settings. Respiratory and hemodynamic measurements were then performed (T30min). Regardless of the response, the concentration was reduced to 10 ppm and after 30 min to 5 ppm. This latter dose was maintained for 3 more h to complete the 4-h trial (T4h). The measurements were performed at the end of each period. According to the protocol, conventional therapy and ventilator settings should not be changed during the 4-h dose-response test. Positive response was defined as an increase in $Pa0_2/Fi0_2$ ratio of 10 mm Hg (26) above the baseline value, with 20 ppm dose at T30min or 5 ppm dose at T4h. If the patient did not respond, iNO was readministered in a starting dose of 40 ppm and an attempt with a dose of 20 ppm was performed every day. Based on a positive response to the dose-response test, iNO was continued at a 5 ppm iNO dose until $Sa0_2$ ≥88% with $Fi0_2$ <0.6 was achieved. The iNO therapy was then withdrawn at gradual decreases of 1 ppm/h over 6-12 h. If withdrawal caused a decrease in $Pa0_2$, requiring an increase of $Fi0_2$ by 20% or more, iNO was reintroduced at the previous

Table 1. Study inclusion and exclusion criteria[a]

Inclusion criteria

A) ARDS defined according to the American-European Consensus Conference (15) as:
- PaO_2/FiO_2 ratio ≤200 (regardless of the amount of Peep)
- Bilateral infiltrates on the frontal chest radiograph
- No clinical evidence of left atrial hypertension

B) Immediately before enrollment: SaO_2 <88% with FiO_2 ≥0.6 and Peep ≥10 cm H_2O

C) Ventilator settings: V_T and Pip limited to 8 mL/kg and to ≤35 cm H_2O, respectively

D) Hemodynamic stability

Exclusion criteria

A) Congenital cardiac disease
B) Chronic lung disease

[a]Abbreviations: ARDS – acute respiratory distress syndrome; FiO_2 – fraction of inspired oxygen; Peep – positive end-expiratory pressure; SaO_2 – arterial saturation of oxygen; V_T – tidal volume; Pip – peak inspiratory pressure.

dose. The aim of this study was to maintain iNO at the lowest dose associated with an improvement in oxygenation. The mean iNO dose and the $Fi0_2$ and Pip levels were assessed at the end of the 4-h dose-response test and at the end of the day of the beginning of iNO treatment (d0) and the following days (d1, d2, d3...).

Statistical Analysis

Normally and non-normally distributed data were expressed as mean±SD and median (ranges), respectively. Friedman's repeated measures of variance test was used to compare the variables at each evaluation time (27). Differences were considered significant at $p<0.05$.

Results

Patients

During the study, 242 patients were admitted at the Pediatric Intensive Care Unit. Ten children, seven girls and three boys (median age, 11 months; range, 1 to 132 months), fulfilled the criteria to be enrolled at the iNO treatment protocol. The patients' clinical characteristics are shown in Table 2. Infections, such as sepsis/septic shock and pneumonia, were the most common causes of ARDS. The patients had severe lung injury with mean lung injury score of 3.2±0.4, and mean PRISM score 22.2±4.6, predicting a mean mortality risk of 43.9±6.6%. Multiple organ system failure was diagnosed in six children when catecholamines were used. The therapy with iNO was introduced as early as possible; the median time between ARDS diagnosis and initiation of iNO therapy was 12 h (1-48 h). The patients had been receiving mechanical ventilation for 1 to 216 h (median, 24.5 h) before enrollment.

Acute Response to iNO therapy

As shown in Table 3, immediately before the beginning of iNO therapy the patients had impaired oxygenation, as shown by the median of the $Pa0_2/Fi0_2$ ratio of 64.6 mm Hg (32.1 to 106) and OI of 29.95 cm H_2O/mm Hg (20.5 to 75). All but one patient had a positive response to the initial iNO dose of 20 ppm at T30min, with an increase of 10 mm Hg in $Pa0_2/Fi0_2$ ratio, according to the protocol. At T4h, oxygenation indexes significantly improved in all patients. The mean percentage improvement in $Pa0_2/Fi0_2$ ratio and OI from baseline was 63.6% and 44.9%, respectively. During the 4-h dose-response test, the heart rate, mean arterial pressure, and $PaCO_2$ did not show any significant variation. By permissive hypercapnia approach, partial arterial pressure of CO_2 values as high as 82 mm Hg (10.9 kPa) were observed. The conclusion of this 4-h study allowed the Pediatric Intensive Care Unit staff to continue iNO administration beyond the dose-response test-period in all children.

Sustained Response to iNO Therapy

The course of the OI over 4-day treatment is shown in Figure 1. Therapy with iNO caused sustained improvement in the OI over the following days of treatment. Also, the ventilator settings indicating risk of ventilator-induced lung injury could be significantly decreased (Table 4). The FiO_2 levels significantly decreased from d0 to d1, and subsequently from d1 to d2 and from d2 to d3. Also, Pip levels were reduced from d1 to d2 and from d2 to d3. As integral part of the ARDS therapeutic strategy, Peep was not changed significantly during the first days of treatment (Table 4). The mean iNO treatment period was 3.3±1.8 days; the mean iNO dose used 2.6±1.03 ppm; and the mean time of mechanical ventilation was 14.2±3.8 days.

There were no serious adverse events during iNO administration: methemoglobin levels did not

Table 2. Clinical characteristics of the patients included in the study[a]

Patient No.	Age (months)/ sex	LIS	ARDS etiology	Other MOSF	PRISM score (mortality risk)	Inotropic support	Outcome
1	84/F	3.0	trauma	CV	20 (49%)	DA; Dob	survived
2	11/F	2.6	pneumonia	–	19 (37%)	–	survived
3	2/M	3.0	pneumonia	–	18 (38%)	–	survived
4	1/F	3.3	pneumonia	–	21 (41%)	–	survived
5	24/F	2.6	trauma	–	15 (35%)	–	survived
6	8/F	3.6	septic shock	CV; C; K; GI	29 (52%)	DA; Dob; NE	died
7	30/M	3.6	septic shock	CV; K; C	22 (42%)	DA; Dob; NE	survived
8	11/M	3.6	septic shock	CV; C	27 (53%)	DA; Dob	survived
9	132/F	3.3	pneumonia	CV	28 (50%)	Dob	survived
10	3/F	3.6	septic shock	CV; C	23 (42%)	DA; Dob	survived

[a]Abbreviations: LIS – lung injury score; ARDS – acute respiratory distress syndrome; MOSF – multiple organ system failure; PRISM – pediatric risk of mortality; F – female; M – male; CV – cardiovascular; C – coagulopathy; GI – gastrointestinal; K – kidney; DA – dopamine; Dob – dobutamine; NE – norepinephrine.

Table 3. Acute effect of iNO on the oxygenation indexes, gas exchange, and hemodynamic variables[a] during the 4-hour dose-response test[b]

	Test times[c]		
Parameter	T0	T30min (20 ppm)	T4h (5 ppm)
$Pa0_2/Fi0_2$ (mm Hg)	64.6 (32.1-106)	95.0* (42.7-165.1)	105.7* (65.5-176)
OI (cm H_2O/mm Hg)	29.9 (20.5-75)	19.4* (10.1-43.4)	16.5* (8-32)
$PaC0_2$ (mm Hg)	49.5 (35.3-82.5)	53.0 (24.6-71.5)	50.3 (21.3-81.7)
HR (bpm)	152.0 (130-165)	150.0 (126-166)	147.5 (126-162)
MAP (mm Hg)	53.5 (45-65)	51.0 (46-60)	55.0 (44-66)

[a]Data expressed as median (ranges).
[b]Abbreviations: iNO – inhaled nitric oxide; T0 – data from baseline; T30min – data at 30 min; T4h – data at four hour; ppm – parts per million; OI – oxygenation index (mean airway pressure x FiO_2 x 100/PaO_2); HR – heart rate; MAP – mean arterial pressure; bpm – beats per minute.
[c]Asterisk indicates $p<0.05$ compared with T0 (Friedman's test).

Table 4. Ventilator settings[a] during iNO treatment[b]

Parameter	Day of treatment[c]			
	d0	d1	d2	d3
$Fi0_2$	1.0 (0.65-1)	0.8* (0.55-1)	0.6*# (0.5-1)	0.5*#‡ (0.4-0.7)
Pip (cm H_2O)	30 (25-35)	29 (26-35)	27*# (22-35)	25*#‡ (20-30)
Peep (cm H_2O)	12 (10-14)	12 (9-13)	11 (7-16)	10 (6-15.5)

[a]Data expressed as median (ranges).
[b]Abbreviations: iNO – inhaled nitric oxide; d0 – period from the end of dose-response test to the end of the day of the beginning of iNO therapy; d1, d2, d3 – the days of treatment; FiO_2 – fraction of inspired oxygen; Pip – peak inspiratory pressure; Peep – positive end-expiratory pressure.
[c]Statistics: *$p<0.05$ compared with d0; #$p<0.05$ compared with d1; ‡$p<0.05$ compared with d2 (Friedman's test).

rise over 1% of total hemoglobin in any child, and the maximum NO_2 concentration was 1.5 ppm.

Discontinuation of iNO caused a "rebound", which increased hypoxemia in two children (Fig. 1, patients 7 and 8). Reintroduction of iNO promptly corrected this manifestation and the therapy could be withdrawn 24 h later.

The only fatal outcome (Table 2, patient 6) was caused by septic shock due to an intestinal infection (*E. coli*). This patient developed disseminated intravascular coagulation, which did not respond to blood factor replacement therapy.

Discussion

Since its first description (28), ARDS has been a therapeutic challenge in pediatric intensive care. The iNO local effects on oxygenation, inflammation, pulmonary hypertension (right ventricular afterload), edema, and capillary permeability may account for its use in ARDS.

Rossaint et al (29) first demonstrated in 10 adult ARDS patients that iNO decreases intrapulmonary shunting and improves arterial oxygenation. The use of iNO in newborn babies seems to be an advance in the management of hypoxemic respiratory failure and primary pulmonary hypertension (30,31). Also,

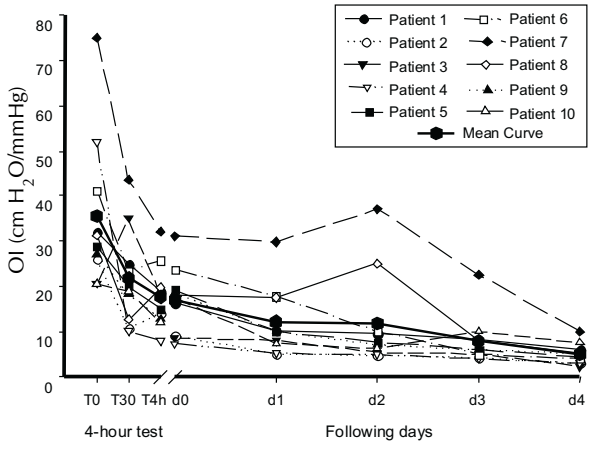

Figure 1.Time course of oxygenation index (OI) during the 4-hour dose-response test and prolonged inhaled nitric oxide (iNO) therapy for each patient, and the mean curve. Sustained improvement could be seen in all patients. Two children (patients 7 and 8) developed "rebound" during the weaning process. T0 – baseline values; T30 – at 30 min with 20 ppm dose of iNO; T4h – end of the test with 5 ppm dose of iNO; d0 – period from the end of dose-response test to the end of the day of the beginning of iNO therapy; d1-d4 – the days of treatment.

Abman et al (32) described in 1994 beneficial effects of iNO on oxygenation and pulmonary hypertension in older children with ARDS.

This is the first study performed in Brazil, aiming to establish a strict protocol for the early use of iNO in children with ARDS.

Patients' Clinical Characteristics

The major causes of ARDS and the age of children included in this study (Table 2) are similar to those in other studies (33-37). All subjects showed evidence of severe lung involvement on radiographic examination and had lung injury score as high as 3.6 (38,39). In relation to the severity of the disease, Demirakça et al (40) found multiple organ system failure in all their patients. Also, the mean PRISM score was 28.4±6.1, predicting a mean mortality risk of 54±15%. In our report, multiple organ system failure was observed in more than half of the patients. The mean PRISM score and mortality risk on admission were also similar to that found by these authors (40).

Administration Protocol and Patient Selection

Since there is no consensus on an acute positive response to iNO therapy, and since many authors state that in a critically hypoxemic patient even a small improvement in oxygenation may be of clinical benefit (41,42), we considered a 10 mm Hg increase in $Pa0_2/Fi0_2$ ratio a positive response. The use of this wider criterion instead of a stricter one (20% increase in $Pa0_2/Fi0_2$ ratio, ref. 43) allowed for more patients to be considered responsive to iNO therapy. Also, it has been recommended that the dose-response test results should be assessed at 4 h, since at that time the patients may have a response that was not present at 30 min (23). One child did not reach our criterion for acute positive response at 30 min, but it did at 4 h. Therefore, patients' response to a dose-response test should be postponed to the end of the test.

It is strongly recommended to use iNO doses lower than 40 ppm in ARDS, since higher concentrations may worsen oxygenation (33-40,44). Presumably, when higher doses are used, penetration occurs in less aerated portions of the lung with a loss of iNO physiological benefits (45). Therefore, according to our protocol, the maximum iNO dose would be 40 ppm during the dose-response test. In children included in our study, however, it was not necessary to use doses higher than 20 ppm.

Ventilator Settings

The administration of iNO results in macro- and microselective effects on the pulmonary vasculature (40). As the macroselective effect is obtained through direct vasodilation of pulmonary arteries, microsele-

ctivity is achieved by the inhalation route that limits the administration of NO to aerated lung regions. This selective vasodilation directs the blood flow from unventilated shunted areas to ventilated but underperfused areas, matching $\dot{V}/\dot{Q}$ and improving oxygenation. This is the so-called "steal phenomenon" (46). However, it has been shown that responsiveness to iNO may be significantly influenced by the application of sufficient Peep (44,47). According to recent recommendations (23), the clinical use of iNO therapy in ARDS must be limited to patients who are *optimally ventilated* with appropriate levels of Peep, which seems to recruit additional alveoli for gas exchange. Therefore, it is fundamental that a clearly defined level of Peep be incorporated into any study that attempts to evaluate iNO therapy. In our protocol, the minimal level of Peep was 10 cm H_2O, but the maximum levels needed were as high as 16 cm H_2O (Table 4). In addition, as a protective lung approach, tidal volume and Pip were limited, permitting high levels of $PaCO_2$.

Acute and Sustained Response to iNO Therapy

Our results show that iNO causes acute improvement in OI in children, as reported by other researchers (33,34,40,44,48). The same results were also found in adults (42,43,49-51). However, there are few reports on OI changes over time in children with ARDS. Acute positive response was expected to be sustained during the entire iNO therapy, but it was very difficult to demonstrate (33,37,43,50). Dobyns et al (48) observed sustained response to iNO vs placebo therapy at 72 h only in subgroups of patients (OI > 25 and the immunocompromised group). These authors explained that iNO therapy did not sustain the improvement in oxygenation in all patients because they were enrolled in the study at the later stages of the disease, as mentioned in other reports (14,41). Experimental studies (51,52) have supported the idea that early iNO treatment could be more effective. Studying adult patients and starting iNO administration within three days of ARDS diagnosis, Dellinger et al (49) observed an improvement in OI over the first four days. Michael et al (50) started iNO therapy in some patients up to 25 days after ARDS diagnosis and observed that improvement in oxygenation was not sustained after 24 h. These authors concluded that the lack of response after 24 h might be due to the fact that the same mechanisms account for the oxygenation improvement with iNO and conventional therapy, and that iNO may only bring them into play earlier. However, the patients with severe disease who were not responding to standard therapy were identified in their inclusion criteria (50).

Unlike other researchers, we started administering iNO after ARDS diagnosis as soon as possible (median, 12 h). In addition to the acute positive response in the 4-h dose-response test, we observed a sustained improvement in oxygenation during four days. We also demonstrated an early decrease in the ventilator settings indicating high risk of baro/ volutrauma, oxygen toxicity (Pip and $Fi0_2$), and a consequent reduction in aggressiveness of mechanical ventilation (Table 4), as reported in other studies (37,40). Our findings may be explained by the early start of iNO administration and the clearly defined criterion for Peep use before NO inhalation.

Another important aspect is that the response to iNO is better with primary (pneumonia) than secondary (sepsis/septic shock) ARDS (43). The reasons for this different response are not clear (43,53,54). Primary and secondary pulmonary injuries were the main causes identified in our study. We were not able to demonstrate any differences in response to iNO therapy between these groups because of the small number of children included.

There are many factors interfering with sustained response to iNO, such as iNO dose, differences between patients, severity of underlying lung diseases, different definitions of significant clinically response, length of respiratory failure before treatment, level of alveolar recruitment during MV, and primary versus secondary ARDS. Difficulties in showing a sustained beneficial effect of NO inhalation may be related to these factors, which are not easy to control in clinical trials.

Many studies do not mention iNO effect on mortality rate in ARDS patients (35,44,48,49,51). This could mean that iNO therapy is worthless. However, the improvement in oxygenation promoted by NO inhalation therapy may contribute to the decrease in mechanical ventilation intensity. This, in turn, may reduce ventilator-induced lung injury, ease the use of new ventilator strategies, including permissive hypercapnia (13), and then positively influence morbidity. We agree with Petros et al (55) on replacement of mortality by morbidity as an end point for evaluation of the role of a new therapy in intensive care environment.

Our study was not designed to assess the effects of iNO therapy on the mortality rate. Only a single death in our study indicates that the early administration of iNO therapy, reducing morbidity in patients with ARDS, may also lead to a decrease in mortality. This hypothesis needs verification in larger controlled trials.

Inhaled NO Weaning and Side Effects

The abrupt withdrawal of NO inhalation produces severe pulmonary vasoconstriction, known as "rebound" phenomenon (43,56). Therefore, it has been recommended that iNO therapy should be slowly decreased to 1 ppm before withdrawal and that the patients should be strictly monitored during the weaning procedure (35,43,56,57). Demirakça et al (40) used OI < 5 cm H_20/mm Hg as a predictor of successful weaning. Two of our children showed "rebound", so we had to increase $Fi0_2$ and restart the iNO during the weaning process.

Toxicity

The iNO toxicity is mainly related to the formation of $N0_2$ and methemoglobin. Nitrogen dioxide is produced spontaneously from NO and oxygen; it contaminates ambient air and produces oxidative damage in terminal bronchioles and proximal alveoli (56). Nitrogen dioxide production rate depends on

the iNO dose, $Fi0_2$, and length of treatment with iNO, the amount of NO_2 formed being 1.1% of the NO dose (58). In our protocol, the administration of the lowest dose of iNO for the shortest period, according to several studies in children (37-39,44,48), did not increase $N0_2$ levels by more than 1.5 ppm.

The reaction of NO with hemoglobin produces methemoglobin. The methemoglobin level above 2% of total hemoglobin can impair the unloading of oxygen and worsen tissue hypoxia. Doses of iNO much higher than those clinically used are not expected to cause significant methemoglobinemia in adults (59). There are only two reports on significant methemoglobinemia during iNO therapy in neonates (60,61). We did not observe methemoglobin levels higher than 1% of total hemoglobin, as was recorded in other studies in children (35-40,44,48). This suggests that iNO is safe for children when used in low doses and with careful monitoring.

Also, iNO therapy can interfere with platelet function and increase bleeding time only in the presence of coagulopathy (62), but the importance of this iNO therapy effect is still unclear. In this study, the only child who died had septic shock with refractory disseminated intravascular coagulopathy, so it was not possible to assess the influence of iNO on coagulopathy.

Study Limitations

Two main limitations of our study were the small number of children and the lack of control group. However, the main aim was to establish a protocol for the early use of iNO together with other current treatments in children with ARDS.

Conclusions

We found acute and sustained response to iNO therapy in children with ARDS, and also observed a decrease in mechanical ventilation intensity during four days. Whether this interferes with morbidity and/or mortality remains to be confirmed. We have also found that iNO administration did not cause any serious adverse effects in our patients.

In view of the complexity of ARDS pathophysiology, it will probably be difficult to find a single therapy for the management of this syndrome. Therefore, iNO therapy must be used with other standard therapeutic approaches to achieve better treatment results. We believe that further randomized controlled trials should concentrate on the early treatment of ARDS, using iNO as part of a routine standard protocol.

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