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

Inhaled Nitric Oxide in Pediatric ARDS

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Abstract

***Aim**: To establish a protocol for the early introduction of inhaled nitric oxide (iNO) therapy in pediatric acute respiratory distress syndrome (ARDS) patients 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) ³ 0.6 and a positive end-expiratory pressure of ³ 10 cm H_2O were included. The acute response to iNO was assessed in a four-hour dose-response test, and positive response was defined as an increase in the PaO_2/FiO_2 ratio of 10 mm Hg above baseline values. Conventional therapy was not changed during the four-hour test. In the following days, patients who had shown positive response continued to receive the lowest iNO dose. Hemodynamic, PaO_2/FiO_2, oxygenation index (OI), gas exchange, and methemoglobin levels were obtained when needed. Inhaled nitric oxide withdrawal followed predetermined rules.*

***Results**: At the end of the four-hour test, all the children showed significant improvement in the PaO_2/FiO_2 ratio (63.6%) and the OI (44.9%) from 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 seen during the study.*

***Conclusions**:1- The iNO causes acute and sustained improvement in oxygenation without adverse effects; 2 - There is an early reduction in ventilator settings during iNO treatment; 3) iNO administration to pediatric patients is safe.*

***Key words**: inhaled nitric oxide, acute respiratory distress syndrome, arterial oxygenation, mechanical ventilation.*

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Acute respiratory distress syndrome (ARDS) is the most severe manifestation and the end spectrum 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 a disruption of the alveolar-capillary barrier with consequent interstitial and alveolar edema. A refractory hypoxemia caused by ventilation/perfusion (V/Q) mismatching and intrapulmonary shunting, and a decrease in lung compliance can be seen[2]. There is also an increase of pulmonary vascular resistance (PVR) which has a quick onset persisting even after correction of hypoxia. The PVR level is correlated with the severity of lung injury and mortality[3]. Right ventricular (RV) failure and low cardiac output may be consequences of pulmonary hypertension (PH)[4].

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

The ARDS pathophysiology 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 PVR 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

Table 1 - Study inclusion and exclusion criteria

Inclusion criteria
A. ARDS defined according to the American-European Consensus Conference[15] as:
   1- A PaO_2/FiO_2 ratio ≤ 200 (regardless of the amount of Peep)
   2- Bilateral infiltrates on the frontal chest radiograph
   3- 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 8mL/Kg and to ≤ 35 cm H_2O, respectively
D. Hemodynamic stability

Exclusion criteria
A. Congenital cardiac disease
B. Chronic lung disease

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.

as the endothelial derived relaxing factor[7,8], and 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 alveoli increases blood flow to these lung areas and preferentially shunt blood away from poorly ventilated regions, matching V/Q and reducing intrapulmonary shunt. This results in improved oxygenation, and reduction of PVR and RV afterload[12]. Improving V/Q matching, iNO may allow less aggressive MV, minimizing 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 pediatric ARDS patients 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.

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, inclusion, and exclusion criteria

Children with ARDS[15], aged between one month and 12 years 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 88-90%. The choice of ventilator was in accordance with the ventilation protocol established by the PICU, depending on the children's weight (less than 10 Kg: Sechrist IV-100B, Sechrist Industries; Anaheim, USA; more than 10 Kg: Inter 5, Intermed; São Paulo, Brazil). Eligibility 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 already mentioned ventilator settings, and a fraction of inspired oxygen ($Fi0_2$) ≥ 0.6 were immediately assigned to the treatment protocol.

The exclusion criteria included patients with congenital cardiac diseases and chronic lung diseases. 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 (IV) infusion of midazolam and/or fentanyl. The patients were paralyzed by the continuous IV infusion of atracurium when necessary. Optionally, prone positioning was used as 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, mean arterial pressure (MAP), and for blood gas sampling. Arterial blood gas was drawn from indwelling catheter for measurement of PaO_2, $PaCO_2$ and SaO_2 as needed. Other biochemical values to

Table 2 –Clinical characteristics of the patients.

Pt. 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

Pt., patient; 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.

calculate pediatric risk of mortality (PRISM) score and to assess coexisting multiple organ system failure (MOSF) were obtained from central venous line. Lung function status was assessed by the oxygenation index (OI: mean airway pressure × $FiO_2 \times 100 / PaO_2$; 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 (MetHb) concentration was measured immediately before and at each arterial blood gas analysis after the beginning of iNO therapy.

Diagnosis of MOSF was based on the criteria proposed by Wilkinson et al.[18] 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 (LIS)[22] were calculated for each patient at enrollment.

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 patients' tracheal tube. Inhaled nitric oxide and nitric dioxide (NO_2) concentrations were measured using an electrochemical sensor (*J P 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 NO_2 concentration. The delivery system was flushed thoroughly before use.

Study design

Patients were enrolled in the study within 1 hour of reaching entrance criteria (Table 1). Baseline measurements (**time zero; T0**) were made at steady-state pressure control ventilation immediately before starting iNO administration. The iNO was administered at a dose-response test of 20 ppm for 30 minutes under the previously mentioned ventilator settings. Respiratory and hemodynamic measurements were then performed (**time 30 minutes; T30min**). Regardless of the response, the concentration was reduced to 10 ppm and after 30 minutes to 5 ppm. This latter dose was maintained for 3 more hours to complete the 4-h trial (**time 4 hour; T4h**). At the end of each period, the data were again obtained. 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 T30mim or 5 ppm dose at T4h. If the patient did not match the criteria for success, a new trial

was attempted with a starting dose of 40 ppm. If the patient did not respond to this, a trial 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 $Sa0_2 \geq 88\%$ with $Fi0_2 < 0.6$ was achieved. The iNO therapy was then withdrawn at gradual decreases of 1 ppm per hour 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 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 from the end of the 4-h dose-response test to the end of the day of the beginning of iNO treatment (d0) and from the following days (d1, d2, d3....) were assessed.

Statistical Analysis

Normally and non-normally distributed data are expressed as mean ± SD and median (ranges), respectively. Friedman Repeated Measures of Variance Test was used to compare the different evaluation times for each variable[27]. Differences were considered significant at a $P < 0.05$.

RESULTS

Patients

Two hundred and forty-two patients were admitted at the PICU during this study. Ten children fulfilled the previous criteria to be enrolled at the iNO treatment protocol. The patients' clinical characteristics are shown in Table 2. The median age was 11 months (1 to 132 months), including seven girls and three boys. Infections, such as sepsis/septic shock and pneumonia, were the most common ARDS etiologies. The patients had severe lung injury with mean LIS of 3.22 ± 0.4, and mean PRISM score 22.2 ± 4.6, predicting a mean mortality risk of 43.9% ± 6.6%. The MOSF was diagnosed in six cases when catecholamines were used. Inhaled nitric oxide therapy was introduced as early as possible; the median duration between the time of ARDS diagnosis and initiation of iNO therapy was 12 hours (1 to 48 hours). The patients had received MV for 1 to 216 hours (median, 24.5 hours) before enrollment.

Acute response to iNO therapy (Table 3)

Immediately before the beginning of iNO therapy, the patients had marked impaired oxygenation demonstrated 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 trial with 20 ppm iNO dose at **T30min** increasing 10 mm Hg in $Pa0_2/Fi0_2$ ratio, according to the protocol. At **T4h**, all patients showed significantly improved oxygenation indexes. The mean percentage improvement in $Pa0_2/Fi0_2$ ratio from baseline was 63.6% and in OI was 44.9%. During the 4-h dose-response test, the heart rate (HR), MAP, and $PaCO_2$ did not show any significant variation. Partial arterial pressure of carbon dioxide values as high as 82 mm Hg (10.9 kPa) were observed using permissive hypercapnia approach. The conclusion of this 4-hour study allowed the PICU staff to continue iNO administration beyond the dose-response test period in all children.

Sustained response to iNO therapy

The time course of the OI over four days of treatment is shown in Figure 1. The iNO therapy 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 were significantly reduced 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 part of the ARDS therapeutic strategy, Peep did not

Table 3 – Acute effect of iNO on the oxygenation indexes, gas exchange, and hemodynamic variables during the four-hour dose-response test.

	Test times		
	T0	T30min (20 ppm)	T4h (5 ppm)
$Pa0_2/Fi0_2$ (mmHg)	64.6 (32.1-106)	95 * (42.7-165.1)	105.7 * (65.5-176)
OI (cmH_2O/mmHg)	29.9 (20.5-75)	19.4 * (10.1-43.4)	16.5 * (8-32)
$PaC0_2$ (mmHg)	49.5 (35.3-82.5)	53 (24.6-71.5)	50.3 (21.3-81.7)
HR (bpm)	152 (130-165)	150 (126-166)	147.5 (126-162)
MAP (mmHg)	53.5 (45-65)	51 (46-60)	55 (44-66)

Data expressed as median (ranges); 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; mm Hg, millimeters of mercury; cm H_2O, centimeters of water; bpm, beats per minute; *$p <$ 0.05 compared with T0 (Friedman's test).

Table 4 – Ventilator settings during iNO treatment

	Days of treatment			
	d 0	d 1	d 2	d 3
$Fi0_2$	1 (0.65-1)	0.8 * (0.55-1)	0.575 *# (0.5-1)	0.5 *#‡ (0.4-0.7)
Pip (cmH_2O)	30 (25-35)	29.2 (26-35)	27 *# (22-35)	25 *#‡ (20-30)
Peep (cmH_2O)	12 (10-14)	12 (9-13)	11 (7-16)	10.1 (6-15.5)

Data expressed as median (ranges); 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 and d3 indicate the days of treatment FiO_2, fraction of inspired oxygen; Pip, peak inspiratory pressure; Peep, positive end-expiratory pressure *$p < 0.05$ compared with d0; #$p < 0.05$ compared with d1; ‡$p < 0.05$ compared with d2 (Friedman's test).

change significantly during the first days of treatment (Table 4). The mean iNO treatment period was 3.3 ± 1.83 days; the mean dose used 2.63 ± 1.03 ppm; and the mean time of MV 14.2 ± 3.8 days.

There were no serious adverse events during iNO administration: methemoglobin levels did not rise over 1% of total hemoglobin in any child, and the maximum NO_2 concentration was 1.5 ppm.

Discontinuation of iNO caused "rebound" which increased hypoxemia in two children (Figure 1, patients 7 and 8). Reintroduction of iNO promptly corrected this manifestation, and the therapy could be withdrawn 24 hours 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 (DIC), which did not respond to blood factor replacement therapy.

DISCUSSION

Since its first description[28], ARDS is still a therapeutic challenge in pediatric intensive care. The iNO local effects on oxygenation, inflammation, pulmonary hypertension (RV 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. In newborn babies, iNO seems to be an advance in the management of hypoxemic respiratory failure and primary pulmonary hypertension[30,31]. This has opened the possibility that iNO can also be an important therapy for older children with ARDS. In 1994, Abman et al[32] described beneficial effects of iNO on oxygenation and pulmonary hypertension in 10 pediatric ARDS patients.

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

Patients' clinical characteristics

Despite the small number of patients in this study, the major etiologies and children's ages (Table 2) are similar to those in other studies[33-37]. All subjects showed evidence of uniformly severe lung involvement in radiographic exam and had LIS as high as 3.6[38,39]. In relation to the severity of the disease, Demirakça et al.[40] found MOSF 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, MOSF 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 patients' selection

In view of the lack of consensus regarding what should be taken as an acute positive response to iNO therapy, and according to many authors who state that in a critically hypoxemic patient even a small improvement in oxygenation may be of clinical benefit[41,42], a 10 mm Hg increase in $Pa0_2/Fi0_2$ ratio was considered to be a positive response. The use of this wider criterion instead of a stricter one (20% increase in $Pa0_2/Fi0_2$ ratio, ref. 43) permitted that more patients could be considered responsive to iNO therapy. It has also been recommended that the dose-response test results should be considered at 4 h, since patients may have a response at that time that was not present at 30 minutes[23]. One of the children did not fulfill our criterion for acute positive response at the first 30 minutes, but achieved it at 4 h. Therefore, patients' response to a dose-response test should be postponed to the end of the trial.

There is a strong trend 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 our cases, however, it was not necessary to use higher doses than 20 ppm.

Ventilator settings

The administration of iNO results in macro and microselectivity ef-

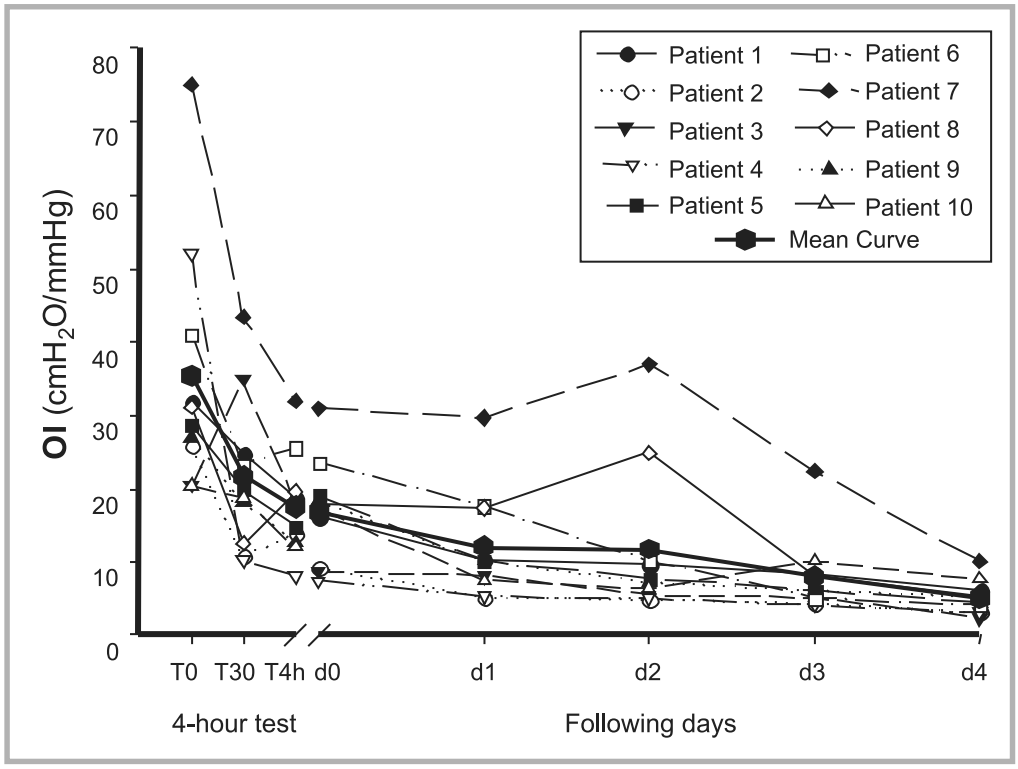

Figure 1 - Time course of oxygenation index during the four-hour dose-response test and prolonged inhaled nitric oxide (iNO) therapy for each patient, and the mean curve. Sustained improvement could be seen in all patients. Two children (patients 7 and 8) developed "rebound" during the weaning process.
T0, baseline values; T30mim, 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.

fects on the pulmonary vasculature[40]. While the macroselective effect is obtained through direct vasodilation of pulmonary arteries, microselectivity 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 V/Q and improving oxygenation, 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 recommendation[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 levels as high as 16 cm H_2O were needed (Table 4). In addition, as a protective lung approach, V_T 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 oxygenation indexes in children, as reported in literature[33,34,40,44,48]. The same results were also found in adults[42,43,49-51]. However, there are a few reports on oxygenation indexes over time in pediatric ARDS patients. It would be expected that the acute positive response could be sustained during the entire iNO therapy, which has been very difficult to demonstrate[33,37,43,50]. Dobyns et al.[48] observed sustained response to iNO versus placebo therapy at 72 h only in subgroups of patients (OI > 25 and in 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 in later stages of the disease, as mentioned in other reports[14,41]. Experimental studies[51,52] have supported the idea that early iNO treatment can be more effective. While studying adult patients and starting iNO administration within three days of ARDS diagnosis, Dellinger et al[49] observed an improvement in oxygenation index 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 hours. These authors reported 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 or conventional therapy and that iNO may only bring them into play earlier. It is important to mention, however, that patients with severe disease, who were not responding to standard therapy, were identified in their inclusion criteria[50].

Differently from previously mentioned reports, we included iNO

as part of our therapeutic approach by starting its administration as soon as possible (median, 12 hours) after ARDS diagnosis. In addition to the acute positive response in the 4-h dose-response test, we observed a sustained improvement in oxygenation during four days (Figure 1). 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 MV aggressiveness (Table 4). This was also observed in other studies[37,40]. Our findings may be explained by the early start of iNO administration and the clearly defined criterion for Peep utilization prior to 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 fully known[43,53,54]. Primary and secondary pulmonary injuries were the main etiologies 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 cases.

In summary, there are many factors interfering with sustained response to iNO: 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 demonstrating a sustained beneficial effect of NO inhalation may be related to these factors, which are not easily controlled in clinical trials.

Lack of demonstrable iNO effect on mortality rate in ARDS patients have been observed in many studies[35,44,48,49,51]. This could mean that iNO therapy is worthless. However, it should be considered that the improvement in oxygenation promoted by NO inhalation therapy may contribute to decrease MV intensity. This, in turn, may reduce ventilator-induced lung injury, facilitate the use of new ventilator strategies, including permissive hypercapnia[13], and then have a positive effect on morbidity. We agree with Petros et al[55] in relation to the replacement of mortality by morbidity as an end point to evaluate the role of a new therapy in intensive care environment.

Our study was not designed to assess the effects of iNO therapy on mortality rate. However, it is important to mention that only one fatal outcome was observed. Therefore, the early administration of iNO therapy, reducing morbidity in patients with ARDS, may lead to a decrease in mortality. This hypothesis needs verification in larger controlled trials.

Inhaled NO weaning and side effects

It has been shown that 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 patients should be strictly monitored during the weaning procedure[35,43,56,57]. Demirakça et al[40] used as a predictor of successful weaning an OI of < 5 cm H_20/mm Hg. Two of our children showed "rebound" and 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 MetHb. Nitrogen dioxide is produced spontaneously from NO and oxygen and contaminates ambient air, producing oxidative damage in terminal bronchioles and proximal alveoli[56]. Nitrogen dioxide production rate depends on the iNO dose, $Fi0_2$, length of treatment with iNO; the amount of NO_2 formed being 1.14% of the NO dose[58]. The administration of the lowest dose of iNO for the shortest period in our protocol did not increase $N0_2$ levels more than 1.5 ppm, according to several studies performed in children[37-39,44,48].

The reaction of NO with hemoglobin produces MetHb. The MetHb level above 2% of total hemoglobin can impair the unloading of oxygen and worsen tissue hypoxia. Doses of iNO far higher than those clinically used are not expected to cause significant methemoglobinemia in adults[59]. Only two reports have been published on significant methemoglobinemia during iNO therapy in neonates[60,61]. We did not observe MetHb levels higher than 1% of total hemoglobin as seen 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.

It has also been described that iNO therapy can interfere with platelet function and increase bleeding time only in the presence of coagulopathy[62]. The importance of this iNO therapy effect remains unclear. In this study, the only child who died had septic shock with refractory DIC, and it was not possible to assess the influence of iNO on coagulopathy.

Study limitations

The main limitation of our study is the small number of cases and lack of control group. However, our main purpose was to establish a protocol for the early use of iNO together with other current treatments in pediatric ARDS patients.

CONCLUSIONS

In this study, we demonstrated acute and sustained response to iNO therapy in pediatric ARDS patients and observed a decrease in MV intensity during four days. If this interferes with morbidity and/or mortality is to be confirmed. We have also concluded that iNO administration did not cause any serious adverse effect on our patients.

In view of the complexity of ARDS pathophysiology, it can be assumed that it will be very difficult to find a single therapy for the management of this syndrome. In contrast, iNO therapy must be used in conjunction with other standard therapeutic approaches for better 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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