RESEARCH BRIEF

Inhaled Nitric Oxide Therapy for Acute Respiratory Distress Syndrome in Children

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The aim of this study was to evaluate the effects of inhaled nitric oxide (iNO) therapy on oxygenation and mortality in children with acute respiratory distress syndrome (ARDS). Thirty-three children with ARDS and an arterial SatO2 <88% despite mechanical ventilation were analyzed. Patients in the iNO group were prospectively enrolled and treated with conventional therapy plus iNO. The control group consisted of retrospectively analyzed patients treated only with conventional therapy. A significant increase in $PaO2/FiO_2$ ratio (25.6%) and decrease in oxygenation index (19.5%) was observed after 4 h of iNO treatment, when compared to baseline values. A positive response to iNO was detected in 69% of patients, and there was no difference between pulmonary and extrapulmonary ARDS. There was no difference in mortality and duration of mechanical ventilation between iNO and control group.

Key words: *Acute respiratory distress syndrome, Children, Inhaled nitric oxide.*

Inhaled nitric oxide (iNO) therapy was shown to improve arterial oxygenation in patients with acute respiratory distress syndrome (ARDS) for the first time in 1993 [1]. Since then, numerous studies have evaluated the use of iNO therapy in adults with ARDS [2-4] while, only one randomized controlled study has been conducted in children [5]. We conducted this study to evaluate the additional benefit of inhaled nitric oxide over conven-tional therapy in terms of oxygenation mortality and duration of mechanical ventilation in children with ARDS.

Methods

Thirty-three children, aged 2-9 years, admitted to the pediatric intensive care unit of University Children's Hospital in Belgrade with ARDS were enrolled in this study. Children were selected if they had arterial $SatO_2$ <88% despite mechanical ventilation (ventilation with low tidal volume [6], FiO_2 >0.6 and PEEP ≥8 cm H_2O). ARDS was defined according to the American-European consensus conference on ARDS published in 1994 [7]. The iNO group comprised of 16 prospectively enrolled patients with ARDS. These patients were treated with conventional therapy plus iNO. The control group consisted of 17 retrospectively analyzed patients who were treated with conventional therapy alone, due to lack of other therapeutic modalities.

The institutional ethics committee approved this study and informed consent was taken before starting iNO therapy. Baseline hemodynamic data, gas exchange values, and ventilator settings were recorded. PaO_2/FiO_2 ratio and oxygenation index were calculated. Following these baseline measurements (M_0), iNO was initially administered during a 4-h response test. In the first 30 min, iNO was given at 20 ppm, and for the next 30 min, the dose was reduced to 10 ppm, regardless of the response. Then the dose was reduced to 5 ppm and maintained for 3 h to complete the 4-h response test. Hemodynamic and respiratory parameters were measured at the end of 30 min ($M_{30\ min}$) and at 4 h ($M_{4\ h}$). The conventional therapy and ventilator settings were not changed during the 4 h. A positive response to iNO was defined as an increase in PaO_2/FiO_2 ratio ≥10 mmHg after 4 h of iNO therapy when compared to the baseline value [8]. In patients who showed a positive response, iNO was continued at 5 ppm and respiratory measurements were further taken at 12 hourly intervals for 72 h. When $SatO_2$ ≥88% was achieved with FiO_2 <0.6, iNO was gradually disconnected over 6-12 h. Methemoglobin levels were assessed during iNO therapy.

iNO was administered following the guidelines and techniques previously described [8,9]. It was delivered through a commercially available delivery device (Pulmonox Mini Messer, Austria), which incorporated

continuous NO and NO_2 monitoring in the distal inspiratory limb.

Conventional therapy included treatment of the underlying illness, mechanical ventilation, hemodynamic support, and administration of inotropes, steroids and nutrition. Regarding mechanical ventilation, a protocol with low tidal volume was used [6], while FiO_2 was adjusted to maintain PaO_2 between 55 and 65 mmHg. All patients were sedated and paralyzed. Surfactant therapy, prone positioning, and recruitment maneuvers were not applied in any patient regardless of the group.

Statistical analyses were performed by using Student *t* test, Wilcoxon rank test, ANOVA with LSD post hoc test, chi-square and Fishers exact test. Differences were considered significant at $P<0.05$.

RESULTS

***Table* I** shows the baseline characteristics of the two groups. The iNO was administered after a median of 17.56 ± 8.51 h from establishing the diagnosis of ARDS, and patients were receiving mechanical ventilation for a median of 29.44 ± 15.91 h before enrollment.

TABLE I COMPARISON OF THE BASELINE CHARACTERISTICS

	iNO group (n=16)	*Control group (n=17)*	*P value*
Age, months	56.5 ± 24.8	58.9 ± 29.0	0.97
Male: Female	7:9	9:8	0.28
ARDS etiology			
Extrapulmonary	8 (50%)	10 (58.8%)	0.39
Pulmonary	8 (50%)	7 (41.2%)	
Primary diagnosis			
Sepsis	8 (50%)	10 (58.8%)	1.49
Pneumonia	5 (31.3%)	4 (23.5%)	
Aspiration	3 (18.8%)	2 (11.8%)	
Near drowning		1 (5.9%)	
MOSF	9 (56.3%)	10 (58.8%)	0.20
Inotropic support	9 (56.3%)	10 (58.8%)	0.20
Steroid therapy	16 (100%)	17 (100%)	
PRISM III score	20.56 ± 4.79	21.82 ± 5.33	0.48
PaO_2/FiO_2, mmHg	57.07 ± 6.96	58.34 ± 5.17	0.56
$PaCO_2$, mmHg	58.19 ± 11.88	53.06 ± 9.85	0.19
PEEP, cm H_2O	10.13 ± 1.15	10.12 ± 0.93	0.98
P_{aw}, cm H_2O	18.62 ±1 .09	18.53 ± 1.12	0.81
OI, cmH_2O/mmHg	33.39 ± 6.82	32.12 ± 4.99	0.55

Date are presented as mean ± SD unless otherwise indicated; iNOG: inhaled nitric oxide group; MOSF: multiple organ system failure; PRISM III score: Pediatric Risk of Mortality score; PEEP: positive end-expiratory pressure; P_{aw}: mean airway pressure; OI: oxygenation index (mean airway pressure x FiO_2 x100/PaO_2; cm H_2O/mmHg).

At the end of the 4-h response test, we observed a significant increase in PaO_2/FiO_2 ratio by 25.6% ($P<0.001$), and decrease in OI by 19.5% ($P<0.001$) as compared to baseline values (***Table* II**). A positive response to iNO was detected in 69% of patients and a significant increase in PaO_2 compared to the baseline value was observed during the initial 12 h ($P<0.001$). There was no difference between pulmonary and extrapulmonary ARDS (45.5% *vs* 54.5%; $P=0.36$).

Twenty-four hours after the onset of iNO therapy, there was no difference in PaO_2 compared to baseline value, and no difference between patients who had showed positive response to iNO and those who did not (***Fig.* 1**). PaO_2/FiO_2 ratio at 12 h, at 24 h and at 36 h, was significantly higher in responders as compared to non-responders ($P<0.001$, $P=0.022$ and $P=0.011$ respectively) and OI at 12 h, at 24 h and at 36 h was significantly lower in responders as compared to non-responders ($P=0.009$, $P=0.028$ and $P=0.031$, respectively).

The median length of iNO therapy was 4.1 ± 0.71 days (range 2.25 – 5.21). No adverse events were noted during iNO treatment. Methemoglobin concentration did not exceed 1% of total hemoglobin. There was no difference in the duration of mechanical ventilation and the use of neuromuscular blockers and length of stay in intensive care between patients in the iNO and control groups. The mortality between patients treated with conventional therapy plus iNO and conventional therapy alone was comparable (43.8% *vs* 47.1%; $P=0.30$).

DISCUSSION

Our results show that iNO acutely improves oxygenation in ARDS patients, which is consistent with other reports in children [5,10] and adults [2-4]. In our study, 69% of patients showed a positive response to iNO, which is

TABLE II EFFECT OF INHALED NITRIC OXIDE (iNO) ON GAS EXCHANGE, RESPIRATORY AND HEMODYNAMIC PARAMETERS DURING 4-H RESPONSE TEST

	M_0	$M_{30\ min}$	$M_{4\ h}$
PaO_2/FiO_2	57.07 ± 6.96	64.71 ± 9.16*	71.68 ± 11.94*†
$PaCO_2$	58.19 ± 11.88	58.25 ± 11.04	55.19 ± 8.36
OI	33.39 ± 6.82	29.53 ± 5.67	26.89 ± 6.09*
HR	137.75 ± 13.47	135.63 ± 13.07	133.31 ± 15.74
MAP	61.50 ± 3.10	60.94 ± 2.95	61.25 ± 2.86

*Date are presented as mean ± SD; M_0: baseline measurements before iNO therapy; $M_{30\ min}$: measurements at 30 min; $M_{4\ h}$: measurements et 4h; OI: oxygenation index; HR: heart rate; MAP: mean arterial pressure; * $P<0.05$ compared with M_0; $^{\dagger}P<0.05$ compared with $M_{30\ min}$.*

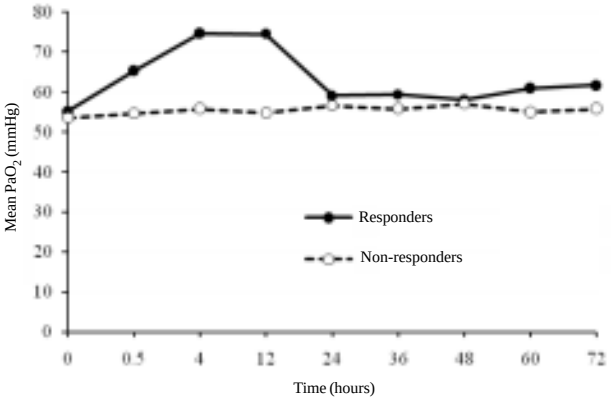

FIG. 1 *Course of PaO_2 throughout 72h in patients with positive response to inhaled nitric oxide therapy and in patients without response to inhaled nitric oxide.*

much less than the 100% response rate reported in other pediatric studies [10,11]. Some studies suggested that the response to iNO was associated with the etiology of ARDS [12]. Rialp, *et al*. observed an increase in PaO_2/FiO_2 ratio only in patients with pulmonary ARDS, while no improvement in oxygenation was seen in extra-pulmonary ARDS [13]. However, in our study, improvement in oxygenation was not affected by the etiology of ARDS.

In addition, we observed a significant improvement in oxygenation during initial 12 h that resolved by 24 h. This initial improvement in PaO_2 allowed for a reduction of FiO_2 and a decreased intensity of mechanical ventilation throughout 36 h, which potentially reduced ventilator lung injury. Dobyns, *et al*. [5] reported a sustained improvement in oxygenation over 72 h, but this effect was observed only in some patients. In another study, Fioretto, *et al*. [10] began early iNO therapy at 1.5 h after ARDS was diagnosed. They observed not only the highest percentage of improvement in PaO_2/FiO_2 ratio, OI, and a response rate of 100%, but also demonstrated a sustained improvement in oxygenation over 4 days. Results of experimental studies also support the idea that early iNO could be more effective [14]. In the present study, we began iNO administration early, in the first 24 h after establishing the diagnosis of ARDS; however; we did not observe a sustained response in oxygenation.

As observed in other studies [2,3,5,10], our results demonstrate that iNO neither reduced the duration of mechanical ventilation nor intensive care stay. In contrast to the study of Fioretto, *et al*. [10], we did not find any differences regarding mortality in pediatric ARDS patients treated with conventional therapy plus iNO and patients treated with conventional therapy alone.

Recently, a systemic review by Afshary, *et al.* [15] showed that iNO transiently improves oxygenation in the first 24h in ARDS patients, but no significant effects of iNO on mortality or other clinical outcomes were observed. Since most of the patients in those studies were adults, they concluded that there is insufficient data to support or refute the routine use of iNO in pediatric ARDS patients.

In conclusion, treatment with iNO improves short-term oxygenation and allows early reduction of ventilator parameters in children with ARDS. This improvement in oxygenation is not influenced by etiology of ARDS. Recognizing the limitations of this study due to small number of cases and retrospective controls, randomized controlled clinical trials are warranted to further verify potential role of iNO therapy in pediatric ARDS.

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WHAT THIS STUDY ADDS?

- Inhaled nitric oxide does not affect long-term outcomes in children with acute respiratory distress syndrome.

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