Outcome of Neonates with Persistent Pulmonary Hypertension of the Newborn Treated with Inhaled Nitric Oxide

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Abstract

Objective : This study assessed the outcome of nitric oxide treatment in infants with persistent pulmonary hypertension of the newborn (PPHN) who failed high frequency oscillatory ventilation (HFOV).

Method : This study was conducted from July 1, 2000 to June 30, 2001 at the neonatal intensive care unit of Queen Sirikit National Institute of Child Health. Nitric oxide was administered to 20 infants, ≥34 weeks gestational age who were diagnosed with PPHN and had two oxygenation index ≥20 at least 30 minutes apart after HFOV treatment.

Results : Nitric oxide inhalation significantly improved the oxygenation index, a/A ratio, A-a gradient ($p<0.05$) and directly measured partial pressure arterial oxygenation. Oxygen saturation improved within ten minutes after nitric oxide inhalation. The survival rate was 85 per cent. Meconium aspiration syndrome was the most common cause of PPHN. No acute complication was found during nitric oxide administration.

Conclusion : Inhalation of nitric oxide increased the blood oxygen tension of infants with PPHN without using a surfactant and ECMO. The authors suggest that inhalation nitric oxide is a useful adjunctive therapy for these patients.

Key word : Nitric Oxide, PPHN, HFOV

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Persistent pulmonary hypertension of the newborn (PPHN) is a complex disorder characterized by marked pulmonary hypertension and altered vasoreactivity, leading to right to left shunting of blood across the patent ductus arteriosus and/or foramen ovale[1,2]. The clinical outcome is very variable because PPHN is associated with many clinical entities[3] such as meconium aspiration pneumonitis, lung hypoplasia, perinatal asphyxia, sepsis, pneumonia, congenital diaphragmatic hernia and surfactant deficiency. PPHN can cause intrapulmonary and extrapulmonary shunting with critical hypoxemia and poor response to high inspired oxygen or phamacologic vasodilatation[4]. High frequency oscillatory ventilation (HFOV) and ECMO (extracorporeal membrane oxygenation) have been advocated as new treatments for infants with severe PPHN[5,6]. The authors have been using HFOV for the management of PPHN since 1997 but the mortality rate was still 70 per cent as shown in Table 1. There is evidence that surfactant deficiency contributes to decreased lung compliance and atelectasis in some patients with PPHN and exogenous surfactant therapy can cause sustained clinical improvement in infants with pneumonia and meconium aspiration syndrome[7,8]. Exogenous surfactant is too expensive for treatment of meconium aspiration syndrome in developing countries. There have been reports that the use of iNO (inhaled nitric oxide) improves oxygenation in neonates with PPHN and reduces the need for ECMO in iNO treated infants[9-12].

The authors treated neonates diagnosed with PPHN who failed HFOV using HFOV plus iNO. The objectives were to assess the survival rate and the results of these strategies.

PATIENTS AND METHOD

A prospective clinical trial was conducted at the neonatal intensive care unit of Queen Sirikit National Institute of Child Health from July 1, 2000 to June 30, 2001. Patients were selected from all infants ≥34 weeks gestational age who required high frequency oscillatory ventilation (SLE 2000 HFO, SLE, UK), name of manufacture, country) for hypoxemic respiratory failure caused by PPHN with clinical diagnosis confirmed by 2-D echocardiogram visualization with right to left shunt at foramen ovale with or without patent ductus arteriosus. The protocol in our unit for treating PPHN with a high frequency ventilator strategy focused on mean airway manipulation to attain a lung expansion of 8.5 to 9 rib radiographically. Cardiotonic agents were used to support cardiac performance and blood pressure when indicated with the use of some paralytic drugs for some patients. When the neonates continued to have hypoxemia and had two oxygenation indexes of ≥20 at least 30 minutes apart, they were eligible for trial. This study was approved by the institutional review board and committee of the Public Health Ministry. Parent consent was also obtained before enrollment in the study. Infants received iNO administration continuously (from INOSYS SLE3600, SLE, UK) *via* an inspired limb starting at 10 ppm and increasing by 5 ppm every 15-30 minutes (max 30 ppm). Exhaled gases, as well as those discharged from the chemiluminescence instrument were scavenged. Methemoglobin and NO_2 levels were monitored for safe values during the trial (methemoglobin ≤4%, NO_2 ≤3 ppm). Mean systemic arterial pressure, postductal arterial blood gases, oxygen saturation, coagulogram and hematocrit were monitored. Arterial-alveolar oxygen tension ratio (a/AO_2) and alveolar-arterial oxygen gradient, (A-a) DO_2 were calculated for each infant. Once the FiO2 was 0.5, iNO was weaned slowly in a decrement of 5ppm every 30 minutes until oxygen saturation was at an optimal level for 3 hours. When the oxygen saturation decreased more than 10 per cent decrement or reached a level less than 85 per cent during weaning from iNO, the authors reintroduced iNO and waited for 24 hours. A case unresponsive to iNO treatment was one without reduction of OI>20 per cent or with PaO_2<80mmHg for 6 hours after enrollment. All survivors received head ultrasound before discharge and were followed at the clinic for one year.

Exclusion criteria

Infants were ineligible for the study if they had uncorrectable cyanotic congenital heart diseases, were maternal anti HIV positive, had congenital anomalies which were incompatible with life or congenital diaphragmatic hernia.

Statistical consideration

Data are presented as mean ± SD. Continuous variables were analysed using *t*-test or Wilcoxon tests. Discrete variables were compared by chi-squared analysis. Multiple two-sided unpaired *t*-test or one-way analysis of variance with repeated measures at

Table 1. Outcome of PPHN at Institute from 1997 to 1999.

Result : case/year, treatment	1997 HFOV or CMV	%	1998 HFOV	%	1999 HFOV	%
Survived	6	30	3	50	6	66.7
Died	14	70	3	50	3	33.3
Total	20		6		9	

CMV = conventional mechanical ventilation,
HFOV = high frequency oscillatory ventilation

Table 2. Demographic data between infants who survived and died.

	Survived	Did not survive	P
Number (case)	17	3	
Male (case)	9	1	0.412
Referred cases	4	1	0.202
Term SGA (case)	2	0	1
GA (week)	38.41 ± 2.74	39.33 ± 1.16	0.580
Maternal age (year)	28.78 ± 4.11	30 ± 1.41	0.685
Apgar 1 minute	6.47 ± 2.23	9 ± 0	-
Apgar 5 minute	8.17 ± 2.16	10 ± 0	-
Birth weight (gram)	2,679.41 ± 293.29	2,933.33 ± 301.38	0.185
Age at diagnosed			
PPHN (hour)	28.47 ± 9.93	23 ± 13	0.4
iNO age (hour)	31.35 ± 10.73	25.67 ± 12.01	0.415

SGA = small for gestational age, iNO = inhalation nitric oxide

a level of significance of $p<0.05$ were used to determine any significant change between those who survived and those who did not, died groups after the treatment.

RESULTS

During the study period, a total of 20 neonates were enrolled. The mortality rate was 15 per cent (3/20). Demographic data showed no statistical significance between the infants who survived and those who did not for birth weight, sex, gestational age, maternal age, Apgar score at 1 or 5 minutes, diagnostic age and nitric oxide inhalation age as shown in Table 2.

Meconium aspiration syndrome was found to be the most common underlying cause among patients (11 cases). Other diagnoses included birth asphyxia (3 cases), pulmonary hemorrhage (2 cases), RDS (2 cases), anemia with shock (1 case) and sepsis with pneumonia (1 case). Death occurred in 3 cases; 2 from MAS and one from birth asphyxia with DIC (disseminated intravascular coagulopathy). Before iNO, there were significant differences in arterial alveolar ratio and alveolar arterial oxygen gradient between the survived and died groups. After patients enrollment with inhalation nitric oxide for 6 hours, there were also a significant differences in oxygen index, arterial alveolar ratio and alveolar arterial gradient between survived and died groups as shown in Table 3.

The authors found response time to improve oxygenation saturation >90 per cent in the range of 10 to 180 minutes in the infants who survived. There was a statistically significant difference in oxygen index, arterial alveolar ratio and alveolar arterial gradient between before and after treatment at 1, 6, 12 hours respectively in the survivors ($p<0.05$) but no statistical significance in those who died as shown in Table 4 and in Fig. 1, 2 and 3 ($p>0.05$) by ANOVA.

Immediate complications seen were bilateral pneumothorax (2), sepsis (1) and pulmonary hemorrhage (1). Both patients with bilateral pneumo-

Table 3. Respiratory parameters of infants who survived and those who died before and after iNO.

Parameter	Survived	Did not survive	P
Before iNO			
OI	56.09 ± 35.10	67.49 ± 27.65	0.573
a/A	0.06 ± 0.025	0.03 ± 0.006	0.0013
(a-A) DO2	623.19 ± 13.705	651.68 ± 10.81	0.028
After iNO 1 hour			
OI	18.86 ± 18.597	29.8 ± 28.026	0.582
a/A	0.26 ± 0.212	0.23 ± 0.24	0.31
(A-a) DO2	500.33 ± 132.24	525.55 ± 160.14	0.821
After iNO 6 hour			
OI	12.64 ± 8.12	79.86 ± 26.93	<0.001
a/A	0.295 ± 0.18	0.05 ± 0.012	<0.0001
(A-a) DO2	476.91 ± 130.09	652.19 ± 10.13	<0.001
After iNO 12 hour			
OI	15.796 ± 14.78	67.36 ± 30.9	<0.01
a/A	0.32 ± 0.22	0.04 ± 0.005	<0.0001
(A-a) DO_2	435.25 ± 186.37	647.64 ± 3.27	<0.0001

Welch 's approximate and unpaired *t*-test at $p<0.05$ is statistically significant.

$PAO_2 = \{(PB-47)(FiO_2)\}-PaCO_2/R$, FiO_2 = fractional inspired oxygen

PAO_2 = partial pressure of O_2 in alveolar gas, PB = barometric pressure = 760 mmHg

R = respiratory quotient = 0.8

$$OI = \text{Oxygenation index} = \frac{MAP \times FiO_2 \times 100}{\text{Postductal } PaO_2}$$

MAP = mean airway pressure

Table 4. Outcome of inhalation therapy in the infants who survived and those who did not.

	Before	After treatment with iNO			P
		1 hour	6 hours	12 hours	
Survived OI	56.09 ± 35.10	18.86 ± 18.597	12.64 ± 8.12	15.79 ± 14.78	<0.05
a/A	0.06 ± 0.03	0.26 ± 0.21	0.29 ± 0.18	0.32 ± 0.22	<0.05
(A-a) DO_2	623.19 ± 13.71	500.33 ± 132.34	476.91 ± 130.09	435.25 ± 186.37	<0.05
Died OI	67.49 ± 27.65	29.8 ± 28.03	79.86 ± 26.93	67.36 ± 30.90	0.22
a/A	0.03 ± 0.006	0.23 ± 0.24	0.05 ± 0.01	0.04 ± 0.005	0.42
(A-a) DO_2	651.68 ± 10.81	525.55 ± 160.14	652.19 ± 10.13	647.64 ± 3.27	0.44

thorax died. Bronchopulmonary dysplasia (BPD) occurred in three cases and two had delayed development and one case had transient hypertension. Monitoring showed methemoglobin level (range 0.1-1.1%), NO_2 (0-0.5 ppm) and coagulogram within normal limits.

DISCUSSION

According to the strategies for management of PPHN in the authors' Institute, early HFOV was used for this condition and could reduce the mortality rate from 70 per cent in 1997 to 50 per cent in 1998 shown in Table 1 as previously reported[13]. In 2000, iNO plus HFOV was used with PPHN cases who failed to have improved oxygenation with HFOV. The present study showed a decrease in the mortality rate in PPHN to 15 per cent consistent with a study done by Kinsella et al[14] showing that a combination HFOV with iNO can improve outcome. Two cases initially responded to iNO but failed because of bilateral pneumothorax and eventually died. The third case did not respond to any treatment because of severe birth asphyxia and DIC and died. Nitric oxide inhalation improves vasodilatation in the non-atelectatic lung[15]. The effect of inhaled NO may be suboptimal when lung volume is decreased in

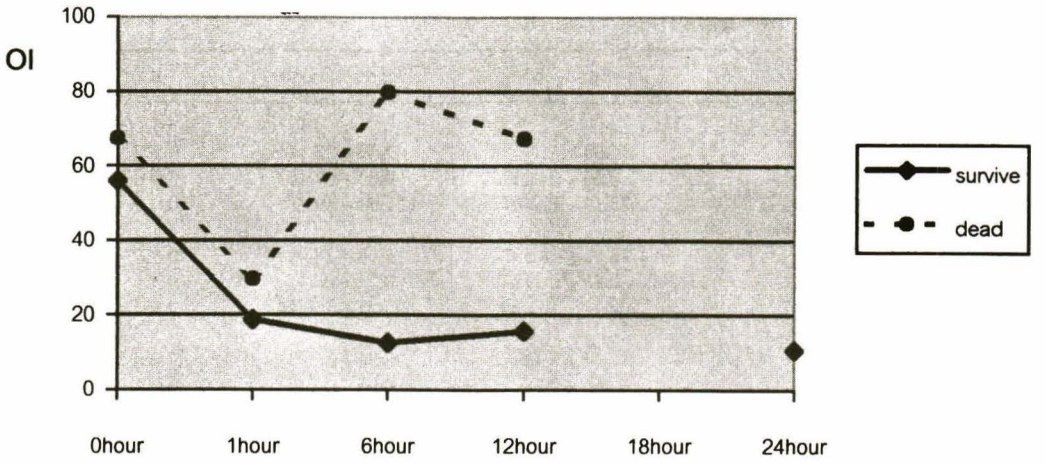

Fig. 1. OI before and after treatment in those who survived and those who died.

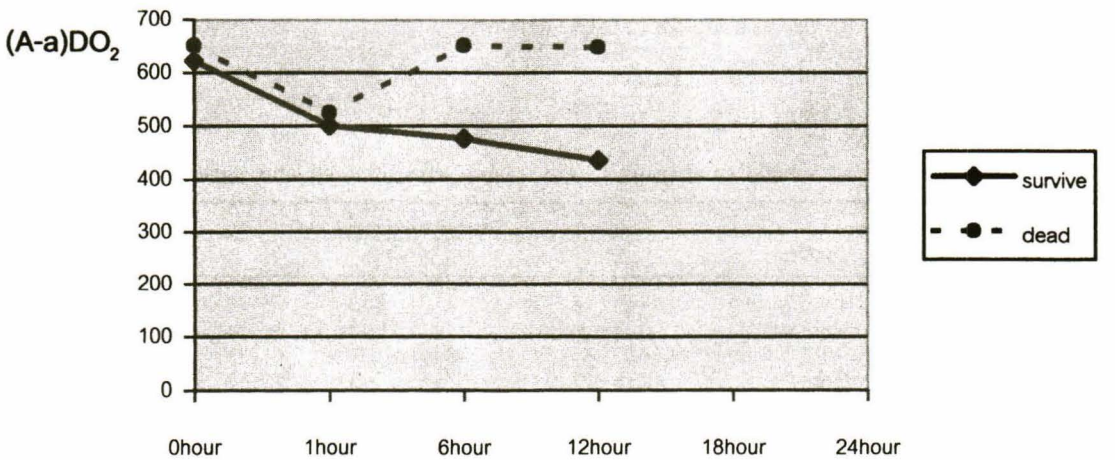

Fig. 2. (A-a) DO_2 before and after treatment in those who survived and those who died.

association with parenchymal lung disease. High frequency oscillatory ventilation helps to achieve optimal lung inflation and minimizes lung injury[13]. Meconium aspiration syndrome was the most common underlying cause of PPHN in the present study and also the most frequent cause of death. In many reports[8,16,17] management of MAS with respiratory failure, using a surfactant can improve oxygenation and decrease the mortality rate but it is not used in developing countries because of the high cost.

The response to iNO varied from 10 minutes to 3 hours and the initiation of iNO was not statistically different betweeen those who survived and those who died (p=0.415). There was a statistically significant difference between those who survived and those who died in a/A ratio and (A-a) DO_2 before and at 6 hours after treatment. This indicates this gas should be used for 6 hours and if there is no improvement in oxygenation, it should be withdrawn. Two survivors developed chronic lung disease even-

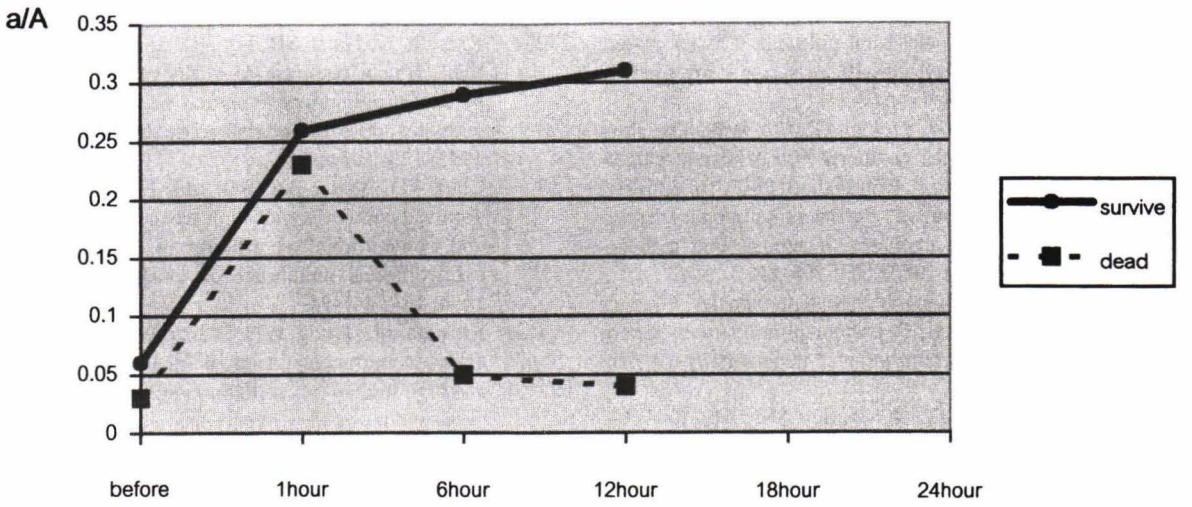

Fig. 3. a/A before and after treatment in those who survived and those who died.

though they were not on intermittent mechanical ventilation for a long time or delayed in diagnosis or treatment. However they had prolonged ventilator use after treatment and we didn't use an additional iNO dose. The authors used a higher dose in only one case in this study (maximum 30 ppm) but no abnormal bleeding time was found. Prolonged bleeding time has been reported at doses of iNO 30 to 300 ppm[18]. Ten cases (50%) had OI>40 before NO inhalation which is usually needed for ECMO management. Nitric oxide used for the presented patients reduced the need for ECMO therapy as in other reports[11,19]. No toxic effects were noted during inhalation of nitric oxide therapy. Occupational health guideline suggest that the upper limit for NO_2 should be 5 ppm[20]. Methemoglobin level and NO_2 were within the safety limit although one case received nitric oxide for 8 days (range 13-192 hour).

SUMMARY

Inhaled nitric oxide combined with HFOV can improve survival in PPHN infants who failed HFOV. No side effects occurred. The authors recommend nitric oxide as a useful adjunctive therapy for PPHN.

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ผลการรักษาภาวะความดันเลือดปอดสูงในทารกแรกเกิดด้วยก๊าซไนตริกออกไซด์

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วัตถุประสงค์การวิจัย : เพื่อศึกษาผลการใช้ก๊าซไนตริกออกไซด์ในการรักษาทารกที่มีความดันเลือดในปอดสูง (PPHN) ที่ไม่ได้ผลหลังให้การรักษาด้วยเครื่องช่วยหายใจความถี่สูง

กระบวนการวิจัย : ได้ทำการศึกษาระหว่าง 1 กรกฎาคม 2543 ถึง 30 มิถุนายน 2544 ในทารกที่รับไว้ในหน่วยผู้ป่วยเด็กหนักทารกแรกเกิดสถาบันสุขภาพเด็กแห่งชาติมหาราชินีอายุครรภ์มากกว่า 34 สัปดาห์ที่ได้รับการวินิจฉัย เป็นความดันเลือดในปอดสูงจำนวน 20 รายที่อาการไม่ดีขึ้นหลังให้การรักษาด้วยเครื่องช่วยหายใจความถี่สูงที่มีค่า oxygenation index >20 จำนวน 2 ค่าห่างกัน ในเวลา 30 นาที ด้วยก๊าซไนตริกออกไซด์

ผลการวิจัย : ทารกที่ได้รับการรักษาด้วยก๊าซไนตริกออกไซด์พบมีการรอดชีวิตร้อยละ 85 และทำให้ทารกมีค่า oxygen index, a/A ratio และ A–a gradient ดีขึ้นอย่างมีนัยสำคัญทางสถิติ ($p<0.05$) และการตอบสนองทางคลินิกในทารกที่รอดชีวิตพบว่าค่า Oxygen saturation ดีขึ้นใน 10 นาที ภาวะการสูดสำลักขี้เทาเป็นสาเหตุที่พบบ่อยร่วมกับภาวะนี้ โดยไม่พบโรคแทรกซ้อนชนิดเฉียบพลันเกิดขึ้นหลังให้การรักษา

สรุป : การให้ก๊าซไนตริกออกไซด์จะเพิ่มระดับ oxygen tension ในเลือดโดยไม่ต้องให้สาร surfactant หรือใช้ (Extracorporeal membrane oxygenation (ECMO) ในการรักษาทารกที่มีความดันเลือดในปอดสูงดังนั้นการให้ก๊าซไนตริกออกไซด์จะมีประโยชน์ในการรักษาทารกที่มีภาวะเหล่านี้

คำสำคัญ : ก๊าซไนตริกอออกไซด์, ความดันเลือดปอดสูงในทารกแรกเกิด, เครื่องช่วยหายใจความถี่สูง

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