Inhaled Nitric Oxide in Newborns with Severe Hypoxic Respiratory Failure

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Background: *Respiratory failure in term and near term infants is often associated with persistent pulmonary hypertension of the newborn and contributes to hypoxemia in these infants. Inhaled nitric oxide (iNO) is currently used as a pulmonary vasodilator to improve oxygenation in neonates with severe respiratory failure.*
Objective: *To determine outcome of administration of iNO in severe hypoxic respiratory failure.*
Material and Method: *The present study was conducted from 1999 to 2004 in the neonatal intensive care unit (NICU) at Queen Sirikit National Institute of Child Health. Patients were selected from all infants ≥ 34weeks gestational age who required high frequency oscillatory ventilation(SLE 2000 HFO,SLE,UK) or conventional mechanical ventilation for hypoxemic respiratory failure caused by PPHN. Diagnosis was confirmed by 2-D echocardiogram visualization with right to left shunt through the foramen ovale or patent ductus arteriosus. Inhaled nitric oxide was given as standard therapy in patients who had two oxygenation indices ≥ 20 at least 30 minutes apart after being on a mechanical ventilator.*
Results: *Fifty-five cases were enrolled and male to female ratio was 22.2 to1. The survival rate was 76.4 percent. Inhaled nitric oxide significantly improved oxygenation index, arterial alveolar oxygen tension ratio (a/A O_2), and alveolar arterial oxygen gradient in survivors at one hour after treatment. The earliest improvement in oxygen saturation was within ten minutes. Meconium aspiration syndrome was the most common underlying cause of PPHN. No acute complication was found during nitric oxide administration. Chronic lung diseases, delayed development and severe hearing loss in long-term follow up were found in 10, 5, and 2 cases, respectively.*
Conclusion: *Inhaled nitric oxide should be used early in severe hypoxic respiratory failure with persistent pulmonary hypertension of newborn and can improve survival rates without any major immediate side effects.*

Keywords: ***N****itric oxide, Persistent pulmonary hypertension, Newborn, High frequency oscillatory ventilation*

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Inhaled nitric oxide (iNO) has been used in Europe to treat a variety of conditions in neonates since 1992, though it has been used most frequently for persistent pulmonary hypertension of the newborns (PPHN)[1,2]. PPHN is a rare and potentially life-threatening condition first described in 1969[3]. It may exists as a distinct disorder or as a complication of other respiratory disorders such as respiratory distress syndrome, bacterial pneumonia, meconium aspiration syndrome or congenital diaphragmatic hernia[4,5]. Since neonates with PPHN have an elevated pulmonary pressure causing a right to left shunt resulting in profound hypoxemia, clinicians have sought a primary pulmonary vasodilator without systemic effects. The identification of endothelial derived relaxing factors as the gas, nitric oxide, raised hopes that such a specific pulmonary vasodilator had been identified[6,7]. There have been reports that the use of iNO improved oxygenation in neonates with PPHN and reduced the need for ECMO (Extracorporeal membrane oxygenation) in iNO treated infants[8-10]. The authors had previously reported a one-year pilot study on the use of iNO in PPHN and found usefulness of this gas as an adjunctive therapy for this condition[11]. The authors now report our five years experience with the use of iNO

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for treatment of neonates with severe hypoxic respiratory failure

Objectives

To determine the outcome of administration of iNO in severe hypoxic respiratory failure.

Material and Method

A prospective clinical trial was conducted in the neonatal intensive care unit (NICU) at Queen Sirikit National Institute of Child Health from 1999 to 2004. Patients were selected from all infants $\geq$ 34 weeks gestational age who required high frequency oscillatory ventilation (SLE 2000 HFO, SLE, UK) or conventional mechanical ventilation for hypoxemic respiratory failure caused by PPHN. Diagnosis of PPHN was confirmed by 2-D echocardiogram visualization with right to left shunt through foramen ovale or patent ductus arteriosus. When indicated specific treatment (surfactant, antibiotics) and supportive treatment (inotropes, muscle relaxant, sedatives, blood products) were given to the neonates. When the neonates continued to have hypoxemia and had two oxygenation indices of $\geq$ 20 at least 30 minutes apart, they were eligible for trial. The present study was approved by the institutional review board. Parent consent was also obtained. 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 chemiluminescence instrument were scavenged. Methemoglobin and NO_2 levels were monitored for safe values during the trial (methemoglobin $\leq$ 4%, $NO_2 \leq$ 3 ppm). Mean systemic arterial pressure, postductal arterial blood gases, oxygen saturation, coagulogram and hematocrit were monitored. Oxygenation indices, arterial alveolar oxygen tension ratio (a/A O_2) and alveolar arterial oxygen gradient were calculated for each patient. Once the FiO_2 was 0.5, iNO was weaned slowly in a decrement of 5 ppm every 30 minutes until oxygen saturation was at optimal level (more than 95%) for 3 hours. When the oxygen saturation decreased more than 10 percent decrement or reached a level less than 85 percent 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 percent or with PaO_2 < 80 mmHg for 6 hours after enrollment. All survivors received head ultrasound before discharge and were followed at the clinic in assessment in development (Denver II) for one year. Chronic lung disease was diagnosis as persistence of clinical features of respiratory distress (tachypnea, retractions and rales)[12]. Gastroesophageal reflux was demonstrated by barium swallowing.

Exclusion criteria

Infants were ineligible for the present study if they had uncorrectable cyanotic congenital heart diseases, were born from an anti HIV positive mother, or had congenital anomalies that were incompatible with life or congenital diaphragmatic hernia.

Statistical analysis

Data are presented as mean $\pm$ SD. Continuous variables were analyzed using paired *t*-test or Wicoxon sign rank tests were appropriate. Discrete variables were compared by Chi-square test or Fisher's exact test. Two-sided, unpaired *t*-test or one-way analysis of variance with repeated measures was used to observe the levels of significant change between those who survived and those who did not survive after treatment.

Results

Fifty-five cases were enrolled in the present study. The mortality rate was nearly 24 percent (13/55). Male to female ratio was 2.2 to 1.Demographic data showed no statistically significant differences between survivors and non survivors groups except for the age of diagnosis and duration of treatment with iNO which were earlier and shorter in the non survivors group than in the survivor group(as shown in Table 1).

Meconium aspiration syndrome was found to be the most common underlying cause among patients (25 cases, 45.4%). The other causes were birth asphyxia (14 cases, 25.5%), secondary respiratory distress syndrome (6 cases, 10.9%), pulmonary hemorrhage (4 cases, 7.2%), sepsis (4 cases, 7.2%), and anemia with shock (2 cases, 3.6%). The most common cause of death was meconium aspiration syndrome (7 cases, 12.7%). Before treatment with iNO, there were no significant differences in oxygenation index, arterial alveolar oxygen tension ratio (a/A O_2), and alveolar arterial oxygen gradient between the survivor and non-survivor groups. However, all the parameters showed significant difference between the groups after treatment with iNO for six hours as shown in Table 2 and Fig. 1. The response time for improvement of oxygen saturation to > 90 percent was as early as 10 minutes in some patients and 85.45% responded to iNO within 12 hours. There was no response to treatment in eight cases as shown in Table 3.The underlying diseases in

Table 1. Data or characteristic between survivors and non survivors groups

Data	Survivors (n = 42)	Non survivors (n = 13)	p-value
BW (g)	2955±0.49	2938±381.10	0.77
GA (wk)	38.45±2.37	39.23±2.05	0.26
Maternal age	28.97±5.24	27.77±10.59	0.58
Apgar 1'	6.29±2.74	6.85±2.73	0.57
Apgar 5'	7.95±2.77	7.69±2.93	0.77
Male (n) (%)	28 (66.7)	10 (76.9)	0.73
Outborn (n) (%)	15 (35.7)	8 (61.5)	0.11
Age at Dx	28.88±15.65	19.21±10.22	0.04*
Age at received iNO (hr)	35.79±20.65	27.13±19.01	0.18
iNO max (ppm)	21.17±4.29	22.58±4.62	0.31
iNO (hr)	88.02±50.73	38.96±48.96	0.003*
Air leak (before iNO)	12	3	1
Air leak (after iNO)	3	5	0.013*

Data were presented as $\bar{X} \pm$ SD, * $p < 0.05$ by unpaired t test, BW = birth weight, GA = gestational age, g = gram, wk = week hr = hour, ppm = part per million, Dx = diagnosis, n = number

Table 2. Oxygen parameters before and after treatment with iNO

Time	Survivors			Non survivors		
	OI	(A-a) O_2	a/A	OI	(A-a)O_2	a/A
Before	52.62±4.89	622.72±2.64	0.06±0.003	55.99±6.97	637.56±4.58	0.049±0.005
After Rx						
1 hr*	26.43±4.07	528.36±19.118	0.21±0.029	34.82±7.35	574.59±28.41	0.126±0.038
6 hr**	17.88±2.59	494.41±20.07	0.26±0.028	49.25±10.03	606.52±18.43	0.091±0.024
12 hr	15.59±2.50	463.02±23.43	0.29+0.03			

* $p < 0.0001$ by ANOVA with repeated measurement between before and after treatment in survivors at 1 hour
** by student t-test $p < 0.05$ between survivors and non survivors groups at 6 hours
OI = oxygenation index = $\frac{\text{MAP x } FiO_2 \text{ x } 100}{\text{Postductal } PaO_2}$
PaO_2 = (PB - 47) (FiO_2) - $PaCO_2$/R, PB = barometric pressure = 760, R = Respiratory quotient = 0.8
FiO_2 = fractional inspired oxygen, PAO_2 = partial pressure of O_2
(A-a) O_2 = alveolar arterial oxygen gradient, MAP = mean airway pressure
a/A = arterial alveolar oxygen tension ratio (a/A O_2)

Table 3. Pattern of response to iNO

Response time	n = 55	Percent
10 min-1 hr	23	41.82
>1-12 hr	17	30.90
Partial response	7	12.73
No response	8	14.55

hr = hour, min = minute
partial response = initial response but failed to sustaine this response

the infants who showed no response were severe birth asphyxia (2 cases), bilateral pneumothorax (2 cases), meconium aspiration syndrome (2 cases), *E. coli* sepsis (1 case), and asphyxia with pneumopericardium (1 case). Air leak syndrome occurred statistically more often in the non survivor than in the survivor group as shown in Table 1. Methemoglobin level, NO_2 level, and coagulogram were within normal limits during this study. In long-term follow up for 1 to 4 years, chronic lung disease, gastroesophageal reflux, severe hearing

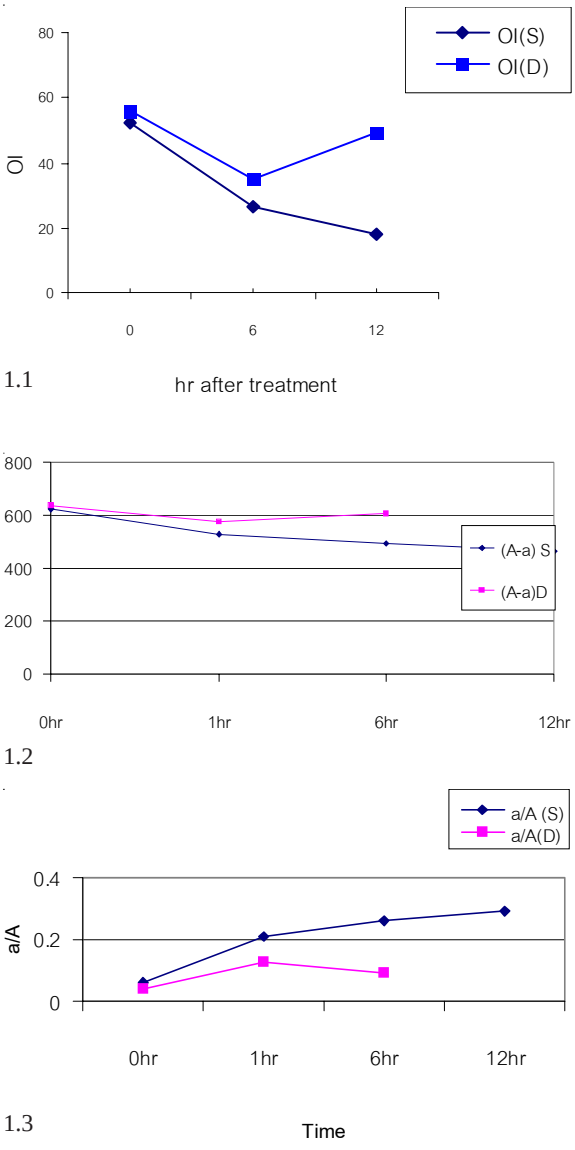

Fig. 1 Comparison of OI, A-a) O2, and a/A between survivors and non survivors
p < 0.05 significant difference at 6 hours after treatment
S = survivor group, D = non-survivor group (dead)

loss, and delayed development were found in 10, 4, 2, and 5 cases respectively.

Discussion

Inhaled nitric oxide has been used in the treatment of PPHN in Queen Sirikit National Institute of Child Health since 1999 and the authors have previously reported the usefulness of this gas as an adjunctive therapy in this condition[11]. The survival rate in the present study was 76.4 percent. This is lower than the previous report because not all cases had been put on high frequency ventilators. High frequency oscillatory ventilation helps to achieve optimal lung inflation and minimizes lung injury[13]. Kinsella et al have shown that HFOV combined with iNO can improve outcome of the treatment[14]. Nitric oxide inhalation improves vasodilatation in the non atelectatic lung[15]. The authors found meconium aspiration syndrome to be the most common underlying cause of PPHN both in the survivor and non survivor groups similar to the other reports[1,11,13,14,16]. The earliest response to iNO was 10 minutes and 85.45 percent of patients responded within 12 hours of treatment. Eight cases who did not respond to iNO such as severe birth asphyxia, air leak syndrome, meconium aspiration syndrome, pneumonia with *E. coli* sepsis, severe birth asphyxia with pneumopericardium, 2, 2, 2, 1, and 1 case, respectively. The respiratory parameters (OI, A-aDO_2, a/A) had significant difference at 1 hours in survivors but was different from the dead group at 6 hours after treatment, as in a previous report[11]. Pneumothorax was significantly more frequent in the non-survivor group than in the survivor group and could be a cause of non response to iNO. In long-term follow up for 1 to 4 years, including 83.33 percent (38 from 42 cases) of the present study group, chronic lung diseases, delayed development, gastroesophageal reflux, and severe hearing loss were found in 10, 5, 4, and 2 cases, respectively. Each patient had more than one complication but thirty-three cases had normal developmental milestone (Denver II). The immediate complications from using iNO gas such as high level of methemoglobinemia and NO_2 were not found.

In conclusion, iNO should be used early in severe, hypoxic respiratory failure with persistent pulmonary hypertension of newborn, which can improve survival rates.

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การรักษาภาวะระบบการหายใจล้มเหลวที่รุนแรงในทารกด้วยก๊าซไนตริกออกไซด์

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ภูมิหลัง: *ระบบการหายใจล้มเหลวที่พบในทารกครบกำหนดและใกล้กำหนดจะสัมพันธ์กับความดันหลอดเลือดปอดสูง และเป็นสิ่งที่ทำให้ผู้ป่วยมีภาวะขาดออกซิเจนเพิ่มขึ้น ปัจจุบันการให้ก๊าซไนตริกออกไซด์ช่วยในการขยายเส้นเลือดในปอดทำให้ออกซิเจนดีขึ้นในทารกที่มีระบบการหายใจล้มเหลว*

วัตถุประสงค์: *เพื่อศึกษาผลการให้ก๊าซไนตริกออกไซด์ในการรักษาทารกที่มีภาวะระบบการหายใจล้มเหลวที่รุนแรง*

วัสดุและวิธีการ: *ได้ทำการศึกษาระหว่าง พ.ศ. 2542 - พ.ศ. 2547 ในทารกที่รับไว้ในหอผู้ป่วยเด็กหนัก ทารกแรกเกิด สถาบันสุขภาพเด็กแห่งชาติมหาราชินีซึ่งมีอายุครรภ์มากกว่า 34 สัปดาห์ที่ได้รับการวินิจฉัยเป็นระบบการหายใจล้มเหลวขณะใส่เครื่องช่วยหายใจความถี่สูงหรือเครื่องช่วยหายใจธรรมดา และวินิจฉัยภาวะความดันเลือดปอดสูงด้วยเครื่อง echocardiogram และมีการให้ยาเพิ่มความดันโลหิต และถ้ามีค่า oxygenation index > 20 ในก๊าซไนตริกออกไซด์รักษาจำนวน 2 ครั้ง ห่างกันในเวลา 30 นาที*

ผลการศึกษา: *พบว่าทารกที่ได้รับการศึกษามีจำนวน 55 รายได้รับการรักษาด้วยก๊าซไนตริกออกไซด์ เป็นเพศชาย 38 รายคิดเป็นอัตราชายต่อหญิง 2.2 ต่อ 1 การตอบสนองต่อการรักษาพบว่ามีการเปลี่ยนแปลงของค่า OI, (A-a) DO_2 และ a/A ในทารกที่รอดชีวิตหลังรักษาแตกต่างจากก่อนรักษาอย่างมีนัยสำคัญทางสถิติใน 1 ชั่วโมง หลังให้การรักษา และการตอบสนองที่เร็วที่สุดจะพบใน 10 นาที การสูดสำลักขี้เทาเป็นสาเหตุที่พบบ่อยที่สุด อัตราการรอดชีวิตคิดเป็นร้อยละ 76.4 จากผลการติดตามภาวะแทรกซ้อนที่เกิดตามมาพบว่ามีทารก 10 รายเป็น chronic lung disease ทารก 5 รายมีพัฒนาการช้า และ 2 รายมีปัญหาการสูญเสียการได้ยินที่รุนแรง การศึกษาครั้งนี้ไม่พบโรคแทรกซ้อนจากการใช้ก๊าซ NO*

สรุป: *การให้การรักษาทารกที่มีระบบการหายใจล้มเหลวที่มีภาวะความดันเลือดในปอดสูงด้วยก๊าซไนตริกออกไซด์ตั้งแต่เริ่มแรกจะช่วยเพิ่มการรอดชีวิตโดยไม่พบข้อเสียของการใช้ก๊าซ*