Inhaled Nitric Oxide Therapy in Premature Infants with Mild to Moderate Respiratory Distress Syndrome

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Abstract

Inhaled nitric oxide (iNO) therapy has been demonstrated to acutely improve oxygenation in preterm infants with severe pulmonary disease. Administration of iNO to the premature infants with less severe pulmonary illness has not yet been studied extensively. Therefore, the authors performed a pilot study enrolling thirty-four premature infants with respiratory distress syndrome (RDS) within 72 hours of age, birth weight between 500-2,000 g, whose oxygenation indexes exceeded our birthweight-specific criteria. Infants were randomly assigned to either treatment with (iNO group; n = 16) or without (control group; n = 18) iNO. Inhaled NO was started at 20 ppm and weaned to 5 ppm over 24-48 hours. Routine cranial ultrasonography was performed and the occurrence of intraventricular hemorrhage (IVH) was interpreted by an attending pediatric radiologist unaware of the treatment group assignment. The study showed that the two groups were of similar birth weight (mean±SEM) : control 901±73 g *vs* iNO 874±70 g; and gestational age : control 27.2± 0.5 wk *vs* iNO 26.8±0.5 wk. Other baseline parameters between the two groups were also similar. The mean ages of the infants at the time of entry were 11.7±2.2 and 8.3±0.9 hours in the controls and iNO group. The entry oxygenation index (OI) did not differ between the two groups: control 11.9±2.2 *vs* iNO 10.8±1.50. After 30 minutes of iNO therapy, there was a 50 per cent increase in partial pressure of oxygen tension (PaO_2) and 15 per cent reduction in OI, ($p = 0.02$ and $p = 0.04$ *vs* baseline, respectively). No statistical difference in the incidence of significant IVH (Grade III and IV) was detected: control 27.8 per cent; iNO 25.0 per cent. The incidence of other acute complications as well as early neonatal death, were comparable between the groups. The mean methemoglobin concentration was 1.2±0.5 per cent. In conclusion, these preliminary data suggest that iNO, as used in

this protocol, acutely improves oxygenation without increasing significant IVH in premature infants with mild to moderate RDS. These important findings serve to justify further study of the efficacy of iNO on long term pulmonary outcome and mortality in this group of infants.

Key word : Inhaled Nitric Oxide, Intraventricular Hemorrhage, Premature Infants, Safety

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Respiratory distress syndrome (RDS) remains a major cause of neonatal morbidity and mortality(1). For decades, antenatal steroids and surfactant replacement therapy have been shown to improve survival of very low birth weight infant suffering from this disease(2). However, many premature infants with RDS show suboptimal response to surfactant treatment and fail to have sustained improvement in oxygenation(3,4). Aggressive mechanical ventilation is still required to correct progressive worsening of hypoxemia, which inevitably places the infants at high risk for additional pulmonary problems, particularly, air leak syndrome and bronchopulmonary dysplasia (BPD). The long-known pathophysiologic mechanism of RDS is characterized by diffuse atelectasis due to surfactant deficiency resulting in intrapulmonary shunting. Recent studies in human premature infants with RDS have shown that pulmonary hypertension can complicate the course of severe RDS in some, which contributing to an increase in mortality despite surfactant therapy(5-7). Postnatally sustained elevation of pulmonary arterial pressure may cause extrapulmonary right to left shunting through the ductus arteriosus and/or the foramen ovale during the acute phase of RDS, and further exacerbate the existing hypoxemia.

Inhaled nitric oxide (iNO), although not being shown to reduce the mortality, has been shown to improve oxygenation and reduce the need for extracorporeal membrane oxygenation (ECMO) in near-term and term infants with severe hypoxemic respiratory failure(8-10). In premature infants with RDS, for whom the ECMO is not an option, the selective pulmonary vasodilator effect of iNO might be beneficial, if anything, to minimize lung injury from mechanically ventilatory management. In animal models, response of vascular smooth muscle cell to exogenous NO is present very early in gestation(11, 12). Recent studies in human premature infants with severe RDS support the effect of iNO in improving oxygenation(13-16). by improving ventilation-perfusion matching. Subdehar et al studied changes in pulmonary hemodynamics in preterm infants with iNO(16). The results showed that iNO significantly decreased pulmonary arterial pressure (PAP) and increased pulmonary blood flow within 30 minutes. The oxygenation improvement was weakly associated with increased pulmonary blood flow, but not with the reduction in PAP. However, no study has yet demonstrated the significant effect of iNO on mortality or BPD. Whether optimal dose and timing of iNO therapy in these tiny infants determine these outcomes remain controversial. A recent study by the authors in ventilated premature infants with RDS has shown significant correlation between initial pulmonary disease severity defined by oxygenation index [OI = (mean airway pressure x fractional inspired oxygen concentration)/partial arterial oxygen

tension (PaO_2)] and the subsequent development of BPD[17]. Interestingly, twenty-nine per cent of infants with initially less pulmonary severity (initial OI of ≤4) even developed BPD. One of the multifactorial mechanisms for the development of BPD, which plays an important role is activation of the inflammatory process following an acute lung injury. The report in preterm lambs with respiratory failure showed that, in addition to the effect on oxygenation, iNO lessened pulmonary edema and decreased lung neutrophil accumulation[18]. From those above observations, the authors hypothesize that, by giving iNO to infants with less severe pulmonary disease or earlier before the process of BPD is far established, iNO may not only improve oxygenation, but ameliorate the inflammatory reaction contributing to the evolution of chronic lung disease. Before testing this hypothesis, the authors conducted a pilot open-labeled trial of iNO in infants <2,000 g with initially less severe pulmonary disease to assess the acute effect on oxygenation and the potential adverse effects of iNO therapy.

MATERIAL AND METHOD

Study population

All mechanically ventilated premature newborn infants with a birth weight less than 2,000 g admitted to the intensive care nursery at the University of Chicago Children's Hospital were considered for the study. Each infant underwent clinical evaluation including history and physical examination. Synthetic surfactant (Exosurf neonatal®) was given, 2 doses as prophylactic therapy in infants ≤1,250 g birth weight, and 3 doses as rescue treatment in bigger infants with documented RDS. Those who were ≤1,250 g also received prophylactic indomethacin (3 doses), 0.2 mg/kg/dose for the first dose, then 0.1 mg/kg/dose at 12 and 36 hours after the first dose for the next 2 doses. Eligible infants were enrolled into the study only after informed consent was obtained from their parents or legal guardians. Infants were considered eligible if they met the following criteria: clinical RDS requiring mechanical ventilation; postnatal age less than 72 hours; oxygenation index (OI) ≥4 in birth weight ≤1,000 g; ≥6 in birth weight 1,001-1,250 g; ≥8 in birth weight 1,251-1,500 g; ≥10 in birth weight 1,501-1,750 g; and ≥12 in birth weight 1,751-2,000 g. In addition, only infants with a systemic arterial catheter to measure systolic, diastolic, and mean systemic arterial pressures were included. Infants with major congenital malformations (except for patent ductus arteriosus and/or foramen ovale) or hydrops fetalis were excluded from the study.

Study design

This was a prospective, randomized noncrossover study, which was approved by the Univer sity of Chicago Institutional Review Board. The study period began in July 1997 and ended in January 1998. After meeting the above entry criteria and informed consent was obtained, enrollment was attempted within 6-12 hours. The patients were randomized by a card-picking scheme into a control group and an iNO treatment group. Since two different types of ventilators have currently been used in the institution as a standard care, conventional ventilator (Bear Cub, Bear Medical systems, Riverside, California) and high frequency oscillatory ventilator; HFOV (SensorMedics model 3100A, SensorMedics Corp., Yorba Linda, Calif.), the ventilator used for each infant in the study was left to the discretion of the attending physician. Optimal ventilator parameters were adjusted by the clinical service prior to the beginning of gas study and throughout the study period to maintain the arterial blood gases within a range where pH was 7.25 - 7.45, PaO_2 50 - 80 mmHg and $PaCO_2$ 40 - 55 mmHg. Patients on HFOV were initially treated without iNO until after achieving optimal ventilator parameters, as determined by the attending clinical physicians or neonatology fellows and confirmed with radiographically chest expansion evaluation, before iNO was started. After recording baseline values of arterial blood gases and hemodynamic variables including pulse oxymetry oxygen saturation and mean arterial blood pressure, patients in the iNO group were then treated with an initial iNO dose of 20 ppm. To assess the acute effect of 30 minutes of treatment, arterial blood gases, and hemodynamic variables were again determined.

After assessing the acute response to the assigned treatment, an attempt was made to wean and stop iNO with the following protocol. The initial dose of iNO was reduced within 6-12 hours to 10 ppm. In infants who tolerated that initial reduction of iNO, weaning was attempted at the concentration of 5 ppm in the next 12 hours. If the PaO_2 decreased by 15 per cent after each reduction, the gas concentration was increased back to the previous concentration and was weaned again in the next 12 hours. After reaching 5 ppm, slow weaning was

attempted 1 ppm a time as tolerated until the gas was discontinued. According to this protocol, the expected duration of iNO therapy would be 72 hours. In infants who did not tolerate this weaning strategy, iNO was kept at the lowest concentration as the infant's tolerable condition. However, the maximum length of iNO therapy was limited to 7 days. During the entire period of iNO administration, the concentrations of NO and nitrogen dioxide (NO_2) were measured continuously by electrochemical technique. (NOx Box, Bedfont Scientific, England). Methemoglobin concentration was also measured once a day until iNO was discontinued.

All infants received cranial ultrasonography within 72 hours of life and the results for possible intraventricular hemorrhage were interpreted by an attending pediatric radiologist unaware of the assigned treatment. Other neonatal complications such as patent ductus arteriosus, pneumothorax, severe air leak syndrome, necrotizing enterocolitis, and neonatal death were also recorded.

Outcome measures

The primary outcome variable was the incidence of severe intraventricular hemorrhage (grade 3 or 4) compared between groups. The secondary outcome variables included actual and percentage change in PaO_2 and OI which better reflects the oxygenation response in relation to concurrent ventilatory support.

Statistical analysis

All outcome variables were compared between groups using the Mann-Whitney U test for continuous data and the χ^2 test or Fisher's exact test for categorical data. Changes in outcome variables were also compared within groups (baseline and post-treatment) using the Wilcoxon signed ranks test. A p-value less than 0.05 was considered statistically significant.

RESULTS

During the study period, one hundred and eight infants with a birth weight less than 2,000 g required mechanical ventilation for RDS. Among these, fifty-seven infants were eligible for the study. Twenty-one infants were excluded before randomization due to early death and parental consent refusal. Two out of thirty-six enrolled infants died before initiating the treatment. The details of all excluded and dropped-off infants are shown in Table 1. The remaining 34 infants were randomized with 16 infants receiving iNO and 18 infants as controls.

Table 1. Distribution of eligible and non-eligible infants.

Character of infants	Number
Mechanically ventilated	108
Non eligible	51
Congenital anomalies	6
Oxygenation index <4 during first 72 h	35
Term IUGR	3
Extubated within 12 h	4
Futile condition	2
Drug depression	1
Eligible	57
Expired before randomization	8
Parental refusal	6
Parental unavailability	6
Mother expired	1
Expired prior to treatment	2
Total infant enrolled	34

There were no differences between the control and iNO groups with respect to baseline characteristics of infants (Table 2). Although the difference was not statistically significant, fewer infants in the iNO group were exposed to antenatal steroids compared with the control group. The time the infants received the assigned treatment was similar in both groups with the mean age within 12 hours after birth. The infants in each group had a comparable substantial degree of pulmonary disease at the time of treatment reflected by the mild to moderate value of oxygenation index.

Within 30 minutes of entry, there was an improvement of oxygenation in infants treated with iNO (Table 3) as shown by the increase in PaO_2, SaO_2 and the reduction in OI. ($p < 0.05$) Although these changes were not statistically different from the control group, the improvement of all these variables from baseline was significant only in the iNO group (almost 50% improvement in PaO_2; $p = 0.02$ and 15% reduction in OI; $p = 0.04$). Interestingly, mean $PaCO_2$ decreased in the iNO group while it increased in the controls, and this difference was also statistically significant. During treatment, hemodynamic status including mean systemic arterial pressure and heart rate were similar in the two groups.

Table 2. Baseline characteristics of studied infants.

	Control (n=18)	Nitric oxide (n=16)	P-value
Birth weight (g)*	901 ± 73	874 ± 70	0.88
Gestational age (weeks)*	27.2 ± 0.5	26.8 ± 0.5	0.57
Male gender (%)	44.4	62.5	0.33
Race - black (%)	89	100	0.49
Inborn (%)	72.2	81.3	0.69
Prenatal care (%)	66.7	56.3	0.73
Antenatal steroid (%)	55.6	31.3	0.19
Caesarean section (%)	66.7	68.8	1.0
Apgar score* - 1 minute	4.6 ± 0.6	3.4 ± 0.5	0.16
- 5 minute	7.3 ± 0.3	6.6 ± 0.3	0.25
Surfactant (%)	100	100	-
Prophylactic indomethacin (%)	88.9	93.8	1.0
HFOV (%)	38.9	43.8	1.0
Age at receiving treatment (h)*	11.7 ± 2.4	8.3 ± 0.9	0.22
Baseline OI*	11.9 ± 2.2	10.8 ± 1.5	0.93

* Values expressed as mean ± SEM
HFOV = high frequency oscillatory ventilation; OI = oxygenation index.

Table 3. Change in respiratory status variables.

Variable (mean ± SEM)	Control (n=18)	Inhaled nitric oxide (n=16)	P-value (control *vs* iNO)
PaO_2 (mmHg)			
Baseline	87 ± 14	72 ± 5	0.99
30 min	82 ± 11	100 ± 10	0.10
% Δ PaO_2	18.4 ± 19.5	45.2 ± 16.8*	0.07
$PaCO_2$ (mmHg)			
Baseline	37 ± 3	40 ± 1	0.10
30 min	39 ± 3	39 ± 2	0.67
% Δ $PaCO_2$	7.7 ± 5.8	-1.8 ± 4.9	0.02
SpO_2			
Baseline	96 ± 1	97 ± 1	0.28
30 min	97 ± 1	99 ± 0.4	0.01
% Δ SpO_2	0.4 ± 0.8	1.9 ± 0.7*	0.20
OI			
Baseline	11.9 ± 2.2	10.8 ± 1.5	0.93
30 min	9.8 ± 1.9	7.9 ± 1.3	0.46
% Δ OI	-8.2 ± 9.2	-15.2 ± 13.5**	0.46

Δ = value changes (time 30'- time 0'); negative value represent changing direction from baseline
* p = 0.04 *vs* baseline; ** p = 0.02 *vs* baseline

The authors were not able to perform cranial ultrasonography before the study entry in all cases since most of the infants were enrolled early within the first day of life. The incidence of IVH shown here was collected from the final ultrasound results after treatment and within 72 hours of life (Table 4). There was no difference in the incidence of IVH grade 3 or grade 4 between the two groups. The overall incidence of severe grade IVH in this population was 26 per cent (28% in the control group and 25% in the iNO group; p = 1.0).

Additional adverse outcomes and mortality were similar between the two groups (Table 5). Four infants died within 7 days of life. Two infants from

Table 4. Incidence of severe grade IVH.

IVH grading	Control		Nitric oxide		P-value
	n	%	n	%	
Grade III	3	16.7	1	6.3	0.60
Grade IV	2	11.1	3	18.8	0.65

IVH = intraventricular hemorrhage

Table 5. Additional adverse outcome.

Adverse outcome	Control		Nitric oxide		P-value
	n	%	n	%	
Gross pulmonary hemorrhage	-	-	-	-	-
Pneumothorax	1	5.6	2	12.5	0.59
Symptomatic PDA	1	5.6	1	6.3	1.0
Indomethacin	1	5.6	0	0	1.0
Ligation	0	0	1	6.3	0.47
Necrotizing enterocolitis	-	-	-	-	-
Nosocomial infection	7	38.9	7	43.8	1.0
Death	2	11.1	2	12.5	1.0

the control group died from massive IVH grade 3, and two in the iNO group died from worsening respiratory failure, of which one infant also had IVH grade 4. The mean methemoglobin concentration was 1.2±0.5 per cent during the period of iNO exposure.

DISCUSSION

This study was performed as a preliminary study for assessing the effect of early iNO therapy on oxygenation and its safety in premature infants who had mild to moderate RDS. The study shows that iNO at a dose of 20 ppm given to premature infants as early as possible in the course of disease significantly increases the PaO_2 without increasing the incidence of intraventricular hemorrhage.

After iNO has been proven effective in improving oxygenation and reducing the need for extra-corporeal membrane oxygenation in term infants with hypoxic respiratory failure, the target of iNO therapy has now moved towards the group of preterm infants with RDS who are not candidates for ECMO. Early reports and case series successfully used iNO as rescue therapy in premature infants with severe respiratory failure unresponsive to full conventional management including surfactant and high frequency ventilation[19,20]. Recently, some investigators have further studied the effect of iNO on oxygenation in preterm infants. Among these studies, only three were randomized controlled trials (RCTs) [16,21,22]. Although different doses of iNO were used in these trials, the result from meta-analysis showed that iNO may have short term improvement in oxygenation in preterm infants with severe RDS [23]. In the present study, all parameters reflecting oxygenation status significantly improved from baseline within 30 minutes of iNO therapy. Although these changes are not statistically significant when compared to controls due to lack of power, they were deemed clinically significant. The magnitude in OI reduction was comparable to a previously reported study. Subdehar et al randomly assigned 44 neonates with less than 32-wk gestation to receive either iNO or dexamethasone, or both. OI had fallen by 17 per cent from baseline in the treated infant within 30 minutes and this change was significantly different from the controls[16].

Although the present findings regarding the effect of iNO on oxygenation may add some significant contribution to previous findings, patient selection was different. The ultimate benefit expected on using iNO in preterm infants is whether it will reduce the long term outcome. In those previous RCTs[16,21,22], they limited the eligible infants to include only moderate to severe cases of respiratory

failure because of the concern regarding the potential adverse effect of iNO on platelet adhesion and the risk of intraventricular hemorrhage in premature infants. Overall initial OI from those trials ranged from 7-26. Unfortunately, no significant advantages on the incidence of BPD and mortality were demonstrated. However, in the study by Kinsella, one beneficial effect observed is the significant reduction in ventilator days among iNO survivors, whereas in the study by Mercier et al from Franco-Belgium collaborative NO trial group, this observation was found only in near term infants not in preterm less than 33 weeks gestational age[21,22]. Another observation from Kinsella's study, though it is not statistically significant, is the trend in reducing the frequency of chronic lung disease[21]. These observations might reflect the potential action of NO in preventing or lessening lung injury. The lack of significance in these substantial benefits is interesting. From the anecdotal data, the authors studied the correlation of initial severity of pulmonary disease and the risk of subsequent development of BPD. It was found that when assessing the pulmonary disease severity by using OI, each unit increment in OI increased risk of BPD by 9 per cent[17]. It is possible that by giving iNO to premature infants with more severe pulmonary disease who have already experienced a substantial process of lung injury, the significant numbers of those who eventually developed BPD may mask the potential preventive effect of iNO on the remaining infants with less severe pulmonary disease.

The duration of exposure to mechanical ventilation prior to initiation of lung injury might also play a role. There have been a few studies examining the cytologic changes of tracheal aspirate in ventilated preterm newborn infants with RDS to facilitate early diagnosis of BPD[24]. The results showed that evidence of the destructive process usually starts between days 0 and 4 characterized by epithelial sloughing. In Kinsella's study, the median age of infants at the time of entry was 30 hours and 27 hours in the iNO group and controls, respectively [21]. Mercier et al enrolled infants at a median age of 1 day[22]. In Subdehar's study, of which the primary objective was different from the former two trials[16], infants were eligible at 96 hours of age if they fulfilled the criteria for chronic lung disease score defined by Ryan et al[25]. It is possible that in those studied infants with moderate to severe respiratory failure, concomitant with exposure to substantial duration of mechanical ventilation, the process of lung injury was accelerated and already took place at the time of entry. Any strategy that fails to intervene before the damaging process is established would yield minimal effect.

In this study, the authors developed birthweight specific oxygenation index as the inclusion criteria in order to recruit a selected group of infants with mild to moderate pulmonary disease. The lower the baby's birth weight, the lower the oxygenation index used in order to minimize the damaging process. The lowest and highest limit of OI used here were based on the authors' aforementioned unpublished data that in infants with OI ≤ 4, twenty-nine per cent of them developed BPD while 57 per cent of infants with OI ≥ 10 did. By using the OI range from 4-10, as per protocol, the infants were eligible and enrolled at a median age as early as 12 hours after birth. This early enrollment would help minimize the process of lung injury.

There is a debate regarding the potential side effects of using iNO in premature infants. Three randomized trials showed no evidence of increased risk of intracranial hemorrhage[16,21,22]. Only one dose-response study by Van Meurs et al showed the 64 per cent incidence of intraventricular hemorrhage with iNO therapy[13]. However, when they compared the historical controls matched for severity of illness, the incidence was similar. In the present study, though without baseline ultrasound findings, the incidence of intracranial hemorrhage was similar between iNO and controls, even given as early as 12 hours of life which is the most unstable period in the clinical course. The low incidence of IVH found in the present study suggests that iNO at the dose ≤ 20 ppm is safe. There are controversies regarding the optimal dose for improving oxygenation in the premature infants. Some available studies found no dose-response effect of iNO at the dose range from 5-20 ppm[13,15], but some studies found that a higher dose may be needed in premature infants[14]. More extensive studies about the optimal dose of iNO on long-term outcome are required.

SUMMARY

The authors have demonstrated from this preliminary data that iNO acutely improves oxygenation in premature infants with mild to moderate respiratory failure. The iNO strategy used in this protocol is not associated with the increased incidence of intracranial hemorrhage even when given as early

as twelve hours of life. The present study is only a preliminary study for an ongoing larger randomized control trial. This encouraging result would justify further study of early iNO therapy in premature infants with less severe disease to evaluate the potential benefit on long term outcome, particularly, BPD and overall mortality.

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การใช้ก๊าซไนตริกออกไซด์รักษาภาวะหายใจล้มเหลวในทารกเกิดก่อนกำหนด

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มีผู้ทำการศึกษาการใช้ก๊าซไนตริกออกไซด์ (inhaled nitric oxide; iNO) บริหารเข้าสู่ทางเดินหายใจแก่ทารกเกิดก่อนกำหนดที่มีภาวะหายใจล้มเหลวอย่างรุนแรง พบว่ามีผลระยะสั้นต่อการเพิ่มระดับออกซิเจนไปสู่เนื้อเยื่อ การศึกษาผลของ iNO แก่ทารกเกิดก่อนกำหนดที่มีภาวะหายใจล้มเหลวในระดับที่ไม่รุนแรงยังไม่เป็นที่แพร่หลาย ผู้ศึกษาได้ทำการวิจัยนำร่องในการใช้ iNO ในทารกเกิดก่อนกำหนดที่มีน้ำหนักแรกเกิดตั้งแต่ 500–2,000 กรัม มีอายุหลังเกิดไม่เกิน 72 ชั่วโมง จำนวน 34 รายที่ได้รับการรักษาด้วยเครื่องช่วยหายใจเนื่องจาก respiratory distress syndrome (RDS) ที่มีอาการรุนแรงน้อยถึงปานกลาง การคัดเลือกผู้ป่วยใช้ oxygenation index (OI) ที่ระดับต่างกันในแต่ละกลุ่มน้ำหนักตัวเป็นเกณฑ์ วิธีการศึกษาได้แบ่งทารกเป็นกลุ่มควบคุมจำนวน 18 ราย และกลุ่มที่ได้รับ iNO จำนวน 16 ราย โดยจะได้รับ NO ในขนาดเริ่มต้น 20 ppm และลดขนาดลงอย่างช้า ๆ จนเหลือ 5 ppm ภายใน 24–48 ชั่วโมง ทารกทั้ง 2 กลุ่มได้รับการตรวจอัลตร้าซาวด์สมองเพื่อเปรียบเทียบอุบัติการณ์ของการเกิดภาวะเลือดออกในช่องเวนตริเคิลสมอง ผลการศึกษาพบว่า ทารกทั้ง 2 กลุ่มมีน้ำหนักแรกเกิดเฉลี่ย (กลุ่มควบคุม 901 ± 73 กรัม เทียบกับกลุ่ม iNO 874 ± 70 กรัม) และอายุครรภ์เฉลี่ย (กลุ่มควบคุม 27.2 ± 0.5 สัปดาห์ เทียบกับกลุ่ม iNO 26.8 ± 0.5 สัปดาห์) ไม่แตกต่างกันทางสถิติ ลักษณะพื้นฐานอื่น ๆ ก่อนและหลังคลอดไม่มีความแตกต่างกันทางสถิติระหว่าง 2 กลุ่ม ทารกมีอายุเฉลี่ยขณะที่เริ่มการรักษาเท่ากับ 11.7 ± 2.2 และ 8.3 ± 0.9 ชั่วโมง ในกลุ่มควบคุมและกลุ่ม iNO ตามลำดับ และมีค่า OI ไม่แตกต่างกันระหว่าง 2 กลุ่ม (กลุ่มควบคุม 11.9 ± 2.2 เทียบกับกลุ่ม iNO 10.8 ± 1.5) การประเมินผลการรักษาภายในเวลา 30 นาที พบว่ากลุ่ม iNO มีค่า PaO_2 เพิ่มขึ้นร้อยละ 50 และค่า OI ลดลงร้อยละ 15 ($p = 0.02$ สำหรับ PaO_2 และ $p = 0.04$ สำหรับ OI เมื่อเทียบกับก่อนรักษา) อุบัติการณ์ของภาวะเลือดออกในช่องเวนตริเคิลสมองไม่มีความแตกต่างกันระหว่าง 2 กลุ่ม โดยพบในกลุ่มควบคุมร้อยละ 27.8 และกลุ่ม iNO ร้อยละ 25 อุบัติการณ์ของภาวะแทรกซ้อนอื่น ๆ และอัตราตายไม่แตกต่างกันระหว่าง 2 กลุ่ม ระดับ methemoglobin ในเลือดของกลุ่ม iNO มีค่าเฉลี่ยเท่ากับร้อยละ 1.2 ± 0.5 โดยสรุป การบริหาร iNO แก่ทารกเกิดก่อนกำหนดที่มีภาวะ RDS ที่อาการรุนแรงน้อยถึงปานกลางตามแนวทางของการศึกษาครั้งนี้ พบว่าทำให้มีผลระยะสั้นต่อการเพิ่มขึ้นของออกซิเจนที่ไปสู่เนื้อเยื่อโดยไม่ทำให้มีอุบัติการณ์ของภาวะเลือดออกในช่องเวนตริเคิลสมองขึ้นเมื่อเทียบกับกลุ่มควบคุม ผลการศึกษาครั้งนี้ช่วยสนับสนุนการศึกษาเพิ่มเติมประสิทธิภาพของ iNO ต่อการช่วยลดความพิการระยะยาว รวมทั้งอัตราตายในทารกเกิดก่อนกำหนดที่มีภาวะหายใจล้มเหลวต่อไป

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