Inhaled nitric oxide theraphy in preterm infants with severe pulmonary distress syndrome – cases presentation

Mihaela Demetrian[1], Georgeta Grecu[1], Andreea Vidru[1], Andreea Calomfirescu-Avramescu[1], Alina Ciuca[2], Anca Panaitescu[3]

[1]Filantropia Clinical Hospital, Bucharest, Romania
[2]"Grigore Alexandrescu" Children's Emergency Clinical Hospital, Bucharest, Romania
[3]"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

ABSTRACT

Respiratory failure in the premature newborn may be complicated by pulmonary hypertension (PAH) that does not always respond to conventional therapies. Conventional therapy for PAH involves: respiratory support, surfactant administration, sedation and / or muscle relaxation and inotropic agents in the most premature patients.
Our experience in nitric oxide therapy in premature infants under 32 weeks dates back approximately 5 years. There were 7 cases of premature infants with respiratory failure who did not respond to conventional methods of therapy. We will present three case reports with hypoxic respiratory failure and severe pulmonary hypertension that responded favorably to nitric oxide therapy.

Keywords: premature infants, pulmonary hypertension, inhaled nitric oxide

BACKGROUND

Since the introduction of pulmonary surfactant, the rates of mortality caused by respiratory failure in preterm infants significantly decreased [1,2]. Nevertheless, there are cases were oxygenation rate is not improved after surfactant therapy. Preterm infants who are on respiratory support present an elevated risk for developing bronchopulmonary dysplasia (BPD), which has a greater long-term impact.

Regulation of vascular tone in cells is done by nitric oxide (NO) [3]. Nitric oxide is produced from L-arginine by one of the three NO synthases. NO activates guanylate cyclase by binding to its heme component which leads to production of guanosine-cyclic monophosphate (cGMP), which is responsible for the vasodilation effect [4]. NO can be combined with inspiratory gases and thereby, be directly carried into peripheral pulmonary alveoli, where it causes local vasodilation.

Pulmonary vascular resistance is adjusted by endogen [5] or exogen [6] NO. Animal experiment models revealed that pulmonary hypertension is decreased by inhalation of nitric oxide. In general, researchers have observed minor or none at all effects over systemic circulation after administration of inhaled nitric oxide (iNO). Studies on adults and on-term newborns have confirmed that iNO produces selective pulmonary vasodilation, reduces pulmonary arterial pressure and improves ventilation/perfusion ratio [7]. In on term newborn infants with hypoxemic respiratory failure, iNO limits the use of ECMO, but does not lower overall mortality [8].

CLINICAL CASES REPORTS

Case 1

We describe the case of a premature infant, born at 31 + 3/7 weeks of gestation with hypoxemic respiratory failure which did not respond to maximal conventional therapy. The pregnancy has been followed up: premature rupture of membranes at 25 weeks of gestation (total time of ruptured membranes: 42 days).

Corticosteroids prophylaxis, antibiotics and tocolytics were administered. Suspicion of chorioamniotitis and pregnancy of uncertain viability at 31 weeks and 3 days. At birth: previously CPAP (Neopuff) following orotracheal intubation in the delivery room, surfactant administered in the first 30 minutes, initially conventional ventilation: SIMV+PSV FiO2 40-50% but with rapid deteriorating respiratory function, chest X-ray: right pneumothorax (in the first 60 minutes), right pleural drainage. 6 hours from birth: SpO2 – 80% - SIMV+PSV (FiO2 80-90%), mixed acidosis: pH 7.01, pCO2 78 mmHg, BB 11 mmol/l, EB – 13.4 mmol/l. Oxygenation index (OI), calculated by the formula: FiO2 x MAP x 100/PaO2 = 55. A second dose of sur-

factant is administered; dopamine + dobutamine for cardiocirculatory support. Echocardiography shows: pulmonary hypertension (PAP 70-80 mmHg), with right-to-left shunt. At 7 hours of birth iNO therapy is initiated beginning with 15 followed by 20 ppm and ventilation is changed to HFOV; 3-4 hours after administering iNO therapy oxygen saturation is more stable > 90%, FiO2 is gradually decreased (70-60-50%) following decrease in iNO administration 18-15-14-10-5 ppm with full cessation after 72 hours of administration. The newborn had remained conventionally ventilated for 4 days following HFNC another 14 days.

Case 2

We report the case of a female preterm infant, delivered at 30 + 1 weeks of gestation by urgent cesarean section because of premature rupture of membranes. She was the first born of a dichorionic diamniotic twin pregnancy (DCDA). At birth: Apgar score 1 min: 5, 5 mins: 8, birth weight: 1380 g. Initially on CPAP, followed by orotracheal intubation. One dose of surfactant was administered, then the newborn was transferred to the neonatal intensive care unit (NICU). At admission: severe general condition, hypotonic-hyporesponsive; oxygen saturation was 93-94% (FiO2 0.45). Blood meconium passed in the first hours after birth; bloody gastric residual aspiration. Blood gas analyses and usual investigations had normal values. Coagulation tests revealed increased prothrombin time and partially activated thromboplastin time. They were corrected by the administration of fresh frozen plasma (FFP).

FIGURE 1. *Case 1 – Chest X-ray – few hours after birth*

FIGURE 2. *Case 1 – Cardiac ultrasound*

FIGURE 3. *Case 2 – Chest X-ray*

In the next few hours, the respiratory function started to deteriorate. Chest x-ray revealed pulmonary effusions, mainly in the left lung and a second dose of surfactant was administered. Head ultrasound was normal. Echocardiography showed patent ductus arteriosus (PDA) and tricuspidian regurgitation (TR) (PAP 40-45 mmHg), but treatment with ibuprofen was stalled due to modified coagulation tests. In the second day of life echocardiography was repeated presenting PDA with pulsatile flux. The coagulation tests became normal, allowing the administration of ibuprofen (first dose 10 mg/kgc). Large spectrum antibiotics were introduced. In the third day of life, general condition continued to deteriorate. Oxygen saturation was 80% during SIMV with FiO2 0.80-0.90. Severe respiratory acidosis (pH 6.93, pCO2 75 mmHg, bicarbonate 11 mmol/l, EB 15.9 mmol/l). A third dose of surfactant and sodium bicarbonate were administered; continuous perfusion with dopamine has been initiated at the same time. Oxygenation index (OI) was 32. Echocardiography revealed severe pulmonary hypertension (PAPs 77-80 mmHg) with right-to-left shunt. Considering the severe pulmonary hypertension and the critical status, we decided to stop the administration of ibuprofen and to start the iNO therapy. INO began from 10 ppm, the newborn being ventilated SIPPV (FiO2 0.95). After one hour iNO was increased to 15 ppm and conventional mechanical ventilation was changed to high frequency oscillation (HFOV). 8 hours later, oxygen saturation and blood gas parameters were improved and we gradually reduced iNO to 13, 10 respectively 7.5 ppm. At the same time conventional mechanical ventilation was reintroduced and FiO2 was gradually decreased to 0.50. After 42 hours of treatment, the echocardiography showed normal pulmonary pressure and PDA with almost full left-to-right shunt. Oxygenation index was 16. INO was gradually lowered, being stopped after 50 hours since the beginning of the treatment. SIMV was continued with FiO2 gradually decreasing, and after 60 hours since the cessation of iNO, the newborn was extubated. Head ultrasound at 32+5 weeks of gestation was normal. A follow-up echocardiography has been done, the last one (at 34 weeks of gestation) presented normal pulmonary pressure, without shunts and PDA closed.

Case 3

We describe the case of preterm infant delivered through cesarean section at 29 2/7 weeks in vertex presentation after premature rupture of membranes at 26 weeks of gestation. At birth: Apgar score 5/6/6, birth weight 1,400 g. Failure of CPAP due to inefficient respiration. The newborn is intubated in the de-

FIGURE 4. *Case 3 – Chest X-ray*

livery room and afterwards a dose of 200 mg/kgc of surfactant is administered followed by HFOV ventilation. In the next hours, oxygen saturation is maintained between 89 and 92% with inspired oxygen concentration of over 60%; hemodynamic instability with noradrenaline and dobutamine support. A second dose of surfactant is administered after 12 hours of life due to frequent desaturations and increased ventilation parameters. No evident amelioration, oxygen saturation stays between 70-80% at an 80% oxygen concentration. Chest x-ray shows normal lung expansion to the ninth rib. Echocardiography showed severe pulmonary hypertension (PAPs 80 mmHg) with right-to-left shunt. Inhaled nitric oxide at 20 ppm simultaneously with HFOV with VG is initiated. Shortly after, oxygen saturation rises to 90% in approximately two hours. The inspired oxygen concentration is gradually lowered, reaching 40%. INO is administered for 72 hours and after 5 days, the newborn is extubated. He remains oxygen-dependent until 35 weeks of life. The echocardiography done at 32 weeks presented a normal aspect, without any signs of pulmonary hypertension.

DISCUSSIONS

Although iNO therapy was approved for the treatment of PPHN in on-term and near-term newborns, the efficiency of this therapy in preterm infants with acute hypoxemic respiratory failure is not certain. The results of this treatment seen in on-term newborn infants cannot be extended over preterm infants mainly because of different physiopathological processes

involved, the selection criteria, and different results. Eligible selection criteria used in iNO studies on on-term newborns have different outcomes in preterm infants where same values of oxygenation index proved to be associated with higher mortality. Although pulmonary arterial pressure is higher in preterm infants with respiratory failure, it rarely inverses the flow through ductus arteriosus. Therefore, the hemodynamic profile of the preterms is different. ECMO is not used in preterm infants because of concerns regarding hemorrhage complications, hence the ECMO criterion cannot be taken into consideration in this case. Experiments using animal models with BPD suggest that a prolonged iNO treatment can modify pulmonary lesions [9]. Inhaled nitric oxide can reduce pulmonary inflammation and improve vascular remodeling in acute preterm lung.

If iNO therapy can decrease the need of ventilatory support then positive effect on the pulmonary lesions can alleviate or even prevent BPD. Nitric oxide generates but also protects from oxidative lesions [10]. Therefore, the effects of iNO therapy over developing lungs need to be closely evaluated before introducing the therapy into clinical practice.

The major concern in preterm infants is the effect of iNO over coagulation. Nitric oxide was proven to increase bleeding time in volunteer adults, and in adults with ARDS [11]. This seems to be cGMP-dependent mechanisms; it is presumed that the cGMP in platelets increases while they are transported through the lungs. Preterm infants have a higher risk of developing intraventricular hemorrhage (IVH), which impacts long-term development. Hence, it is important that studies should evaluate the effect of iNO therapy in terms of IVH incidence in preterm infants. A few case reports and case series published before randomized controlled studies (RCT) have shown that in preterm infants with severe respiratory failure, who show no response to conventional treatment, including surfactant administration and high-frequency ventilation, oxygenation ratio can be improved with iNO [12]. Mortality and incidence of IVH were namely researched in these studies.

More recent studies on animal models which focus on the direct effect of iNO in protecting the premature lung against the side effects of hyperoxia [13] and sustaining microvascular growth suggest that there may be possible direct benefits for reducing BPD. Other systematic reviews published about iNO in premature infants are inconclusive.

Inhaled nitric oxide (iNO) was approved for treatment of persistent pulmonary hypertension of the newborn (PPHN) in term and near-term newborns. Its selective vasodilating effect on pulmonary circulation was proven to improve oxygenation and reduce the need of ECMO (extracorporeal membrane oxygenation) [14-20].

On the other hand, its role in hypoxemic respiratory failure due to pulmonary hypertension in preterm newborns remains unclear. There are yet no guidelines or standardized protocols, but some studies have shown that iNO can be used as last resort therapy in preterm newborns with severe pulmonary hypertension who are unresponsive to maximal conventional therapy [21-25].

Different studies have shown that iNO can be used as last resort therapy in preterm infants with severe pulmonary hypertension [8,9]. It seems that the response to iNO is significantly improved upon higher gestational age: newborns aged 29 weeks or older have a higher rate of response to iNO than the ones under 29 weeks [10]. The most recent studies conclude that iNO therapy can improve oxygenation rates in extremely premature newborns with PPHN, but it is not usually recommended and needs to be carefully addressed. Moreover, researchers suggest that $FiO_2 >$ 0.65, PPHN diagnosed by echocardiography and birth weight > 750 g are independent predictors of iNO therapy with positive results in preterm newborn infants with respiratory distress syndrome (RDS). The cause of pulmonary hypertension in our patients may be difficult to be established, but it is probably a result of the changes in the pulmonary flows (with a higher vasoconstrictive component) secondary to a maternal factor such as PPROM [10]. However, we cannot exclude that ibuprofen administered for PDA closure was one trigger for pulmonary hypertension. Actually, pulmonary hypertension is a rare side effect, but potentially lethal in premature newborns who receive ibuprofen for PDA closure [26,27].

CONCLUSIONS

Our unit does not have a standard protocol regarding iNO use in preterm newborns. INO therapy is being used as a last resort therapy in preterm newborns with PPHN when maximal conventional therapy has been used (FiO_2 0.80-0.90) and failed.

Furthermore, it should be underlined the way in which the general condition of the patients improved when iNO therapy was associated with HFOV, better than with conventional mechanical ventilation, confirming the efficiency of association between iNO and HFOV for treatment of PPHN.

In conclusion, our experience confirms the fact that iNO treatment must be taken into consideration as a last resort therapy in preterm newborns with acute hypoxemic respiratory failure caused by severe pul-

monary hypertension. Further research and clinical studies should be conducted in order to better determine the real efficiency of this therapy especially in extreme preterm newborns and create standard clinical guidelines and protocols.

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