Acute Respiratory Distress Syndrome (ARDS) in Preterm Infants with Severe Fetal Anemia: 2 Case Reports and Review of Literature

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Abstract

Background: Acute Respiratory Distress Syndrome (ARDS) is an entity not well recognized in the NICU and possibly mis-classified as severe RDS.

Case report: We report two premature infants severely hypoxic at birth refractory to usual treatment of RDS who responded to neuromuscular blockade and prone position which have been proven to be effective in adult and child ARDS.

Conclusion: A consensus definition, as well as criteria for the diagnosis of ARDS in the neonatal population is needed. A standard definition would allow comparisons to the adult and pediatric literature, as well as furthering research on the pathophysiology, epidemiology and effective management of ARDS in the neonatal population.

Keywords: Acute respiratory distress syndrome; Preterm infants

Abbreviations:

ARDS: Acute Respiratory Distress Syndrome; SFR: Sinusoidal Fetal Rhythm; PSA: Peak Systolic Velocity; OI: Oxygen Index; NO: Nitric Oxide; HFOV: High Frequency Oscillatory Ventilation; RDS: Respiratory Distress Syndrome; FMH: Foetal-Maternal Hemorrhage; PPHN: Persistent Pulmonary Hypertension; CMV: Cytomegalovirus; CRP: C Reactive Protein; RBC: Red Blood Cell; MOF: Multiple Organ Failure; VILI: Ventilator-Induced Lung Injury; PEEP: Positive End-Expiratory Pressure

Introduction

We report two similar cases of premature infants who presented antenatally with diminished fetal movements and sinusoidal fetal heart rate. Both infants were profoundly anemic at birth, and developed severe hypoxia with pulmonary hypertension, and responded poorly to repeated doses of surfactant. The clinical features were analogous to ARDS (Acute Respiratory Distress Syndrome) as described in older children and adults.

Case 1

Our first patient was an infant female born at 31 weeks gestational age with a weight of 1500 g. She was born by caesarean delivery with spinal anesthesia performed for Sinusoidal Fetal Rhythm (SFR), decreased fetal movements and high Peak Systolic Velocity (PSA) Doppler of both mean cerebral arteries which was strongly suggestive of severe fetal anemia. The mother was a 26 year old, gravida 1, para 1. The parvovirus serology (IgM and IgG) was negative. The pregnancy was uncomplicated. Betamethasone was not completed and the mother did not have vaginal bleeding. Apgar scores were 2 at 1 mn, 2 at 5 mn and 7 at 10 mn. The amniotic liquid was clear. The infant required endotracheal intubation at birth for absent of respiratory effort after positive-pressure ventilation. Cord pH was 7.15. She was flat, had pale skin and was severely hypoxic. The heart rate was 122 bpm and the mean blood pressure was at 51 mmHg. She was not hydropic. The hemoglobin was at 16 mg/dL with a platelet count at 100 × 10⁹/L and reticulocytes at 297 × 10⁹/L. She received three repacked red blood cell transfusion of 10 cc/kg (RBC) and one platelet transfusion in the first 12 hours of life.

Her arterial gas revealed severe metabolic acidosis (PH: 6.87, bicarbonates: 11 mmol/L, base excess: 21, PCO₂: 52 mmHg and lactates: 15). At that time, she was on conventional mechanical ventilation with Oxygenation Index of 15 and FiO₂ at 100%. Pulmonary hypertension (PPHN) was clinically suspected due to a saturation gradient pre and post ductal of 10%, confirmed by cardiac ultrasound at the bedside. The first chest x-ray showed diffuse white lungs bilaterally. She was switched to high frequency oscillatory ventilation (HFOV) with Mean airway pressure at 16, amplitude at 25 and frequency at 9 Hertz. Inhaled Nitric oxide (NO) was started at 20 ppm with FiO₂ of 100%. She received a drip of fentanyl at 1 mcg/kg/h.

She received two doses of surfactant at 1 hour and 5 hours of life without any improvement. While the baby was at 100% of FiO₂, she responded to neuromuscular blockade and prone position which have been proven to be effective in adult and child ARDS. The infant required repeated doses of surfactant at 1 hour and 5 hours of life. The chromosomal and the genetic profile were normal. The cranial ultrasound, the renal and the liver function were normal. The maternal parvovirus serology (IgM and IgG) was negative. The baby was weaned from NO and mechanical ventilation progressively and reached 45% at 10 hours of life. The remaining neonatal period was uneventful. The hemoglobin level at the discharge time was 109 mg/dl.

Case 2

The second patient was an infant boy born at 33 weeks gestational age with a weight of 1500 g. The pregnancy was uncomplicated. Betamethasone was completed and the mother had no vaginal bleeding. Apgar scores were 2 at 1 mn, 2 at 5 mn and 7 at 10 mn. The amniotic liquid was clear. The infant required endotracheal intubation at birth for absent of respiratory effort after positive-pressure ventilation. Cord pH was 7.15. She was flat, had pale skin and was severely hypoxic. The heart rate was 122 bpm and the mean blood pressure was at 51 mmHg. The infant was born by caesarean delivery with spinal anesthesia performed for Sinusoidal Fetal Rhythm (SFR), decreased fetal movements and high Peak Systolic Velocity (PSA) Doppler of both mean cerebral arteries which was strongly suggestive of severe fetal anemia. The mother was a 26 year old, gravida 1, para 1. The parvovirus serology (IgM and IgG) was negative. The pregnancy was uncomplicated. Betamethasone was not completed and the mother did not have vaginal bleeding. Apgar scores were 2 at 1 mn, 2 at 5 mn and 7 at 10 mn. The amniotic liquid was clear. The infant required endotracheal intubation at birth for absent of respiratory effort after positive-pressure ventilation. Cord pH was 7.15. She was flat, had pale skin and was severely hypoxic. The heart rate was 122 bpm and the mean blood pressure was at 51 mmHg. She was not hydropic. The hemoglobin was at 16 mg/dL with a platelet count at 100 × 10⁹/L and reticulocytes at 297 × 10⁹/L. She received three repacked red blood cell transfusion of 10 cc/kg (RBC) and one platelet transfusion in the first 12 hours of life. The first arterial gas revealed severe metabolic acidosis (PH: 6.87, bicarbonates: 11 mmol/L, base excess: 21, PCO₂: 52 mmHg and lactates: 15). At that time, she was on conventional mechanical ventilation with Oxygenation Index of 15 and FiO₂ at 100%. Pulmonary hypertension (PPHN) was clinically suspected due to a saturation gradient pre and post ductal of 10%, confirmed by cardiac ultrasound at the bedside. The first chest x-ray showed diffuse white lungs bilaterally. She was switched to high frequency oscillatory ventilation (HFOV) with Mean airway pressure at 16, amplitude at 25 and frequency at 9 Hertz. Inhaled Nitric oxide (NO) was started at 20 ppm with FiO₂ of 100%. She received a drip of fentanyl at 1 mcg/kg/h.

She received two doses of surfactant at 1 hour and 5 hours of life without any improvement. While the baby was at 100% of FiO₂, she responded to neuromuscular blockade and prone position which have been proven to be effective in adult and child ARDS. The infant required repeated doses of surfactant at 1 hour and 5 hours of life. The chromosomal and the genetic profile were normal. The cranial ultrasound, the renal and the liver function were normal. The maternal parvovirus serology (IgM and IgG) was negative. The baby was weaned from NO and mechanical ventilation progressively and reached 45% at 10 hours of life. The remaining neonatal period was uneventful. The hemoglobin level at the discharge time was 109 mg/dl.
Case 2
The second case was an infant female born at 32 weeks gestational age with a weight of 1640 g. She was born by caesarean delivery with spinal anesthesia performed for sinusoidal fetal rhythm (SFR), decreased fetal movements and high peak systolic velocity (PSV) Doppler in both mean cerebral artery and was strongly suggestive of severe fetal anemia. The mother was a 31 year old, gravida 1, para 1. The parovirus serology (lgM and lgG) were negative. The pregnancy was uncomplicated. Betamethasone was not completed and the mother did not have vaginal bleeding. The amniotic liquid was clear. Kleihauer-Betke test was positive and suggestive of severe foeto-maternal hemorrhage (FMH) with 52 mL of estimated foetal blood loss. Apgar scores were 2 at 1 mn, 4 at 5 mn and 5 at 10 mn. The infant required endotracheal intubation at birth for absent of respiratory effort after positive-pressure ventilation. The cord pH1 was not drawn. She was hypotonic, had pale skin and was severely hypoxic. The Heart rate was 171 bpm and the mean blood pressure was at 25 mmHg. She was not hydropic. The hemoglobin was at 26 mg/dl with platelet at 110 × 109/L and reticulocytes at 250 × 109/L. She received three packed red blood cell (RBC) transfusion of 10 cc/kg and one platelet transfusion. The first arterial gas revealed severe metabolic acidosis (PH:7.07, bicarbonates: 11 mmol/L, Base excess:-18.7, pCO2:37 mmHg, pO2:39 and lactates: 11). At that time she was on mechanical conventional ventilation with Oxygenation Index at 33 and FiO2 at 100%. She was switched to high frequency oscillatory ventilation (HFOV) with Mean airway pressure at 22, amplitude at 35 and frequency at 10 Hertz. Pulmonary hypertension was clinically suspected due to a saturation gradient pre and post ductal of 10%, confirmed by cardiac ultrasound at the bedside. Nitric oxide (NO) was started at 20 ppm with FiO2 at 100%. The chest x-ray showed diffuse opacification of both lungs. Umbilical venous and arterial lines were inserted and a drip of fentanyl at 1 mcg/kg/h was started. A first dose of surfactant was tried and stopped immediately because profound desaturation. She had hypotension well controlled with dopamine (7 mcg/kg/min). A second administration of surfactant at 2 hours of life, in bolus with faster delivery was well tolerated but did not have any effect on oxygen need. At 26 hours of life, the baby was at 100% of FiO2, on HFOV with a mean airway pressure of 22, NO at 20 ppm, a drip of dopamine and fentanyl. The baby was placed in the prone position and the FiO2 decreased from 100 progressively to 60%. At 36 h of life, the FiO2 increased again to 100% and the baby was saturating at 80%. One dose of muscle paralytic (Rocuronium: 1 mg/kg) was given and immediately the need of oxygen decreased to reach progressively 50%. She received intermittent intravenous dose of hydrocortisone (dose: 1 mg/kg q 6 h). Toxoplasmosis and CMV serologies, C-reactive protein, enteroviral and blood cultures, and the direct coombs test were negative. There was no alpha thalassemia on hemoglobin electrophoresis. The placenta was normal. Head ultrasound, as well as renal and liver function test was normal. She was weaned from dopamine, NO and mechanical ventilation progressively and extubated 5 days later. The remaining neonatal period was uneventful and she was discharged home at 37 weeks corrected gestational age. Her clinical exam before the transfer was normal and the hemoglobin level at the discharge time was 110 mg/dl.

Discussion
Our two preterm infants had respiratory failure associated with PPHN and poor surfactant response. They responded to prone position and neuromuscular blockade which are reported to decrease mortality in child ARDS. This may reflect the complex pathogenesis sequence of ARDS in our preterm infants rather than of neonatal respiratory distress syndrome (RDS). Although the majority of immature infants have a rapid and sustained response after one dose of surfactant with an improvement in oxygenation and gas exchange, a subgroup of infants have a suboptimal response or an early relapse. It was hypothesized that ‘poor responders’ and babies with an early relapse after surfactant administration may have an underlying inflammatory disease process that could affect the alveolar-capillary integrity and induce surfactant inactivation and dysfunction [1]. ARDS is a form of hypoxemic respiratory failure that is characterized by severe impairment of gas exchange and lung mechanics, with a high case fatality rate [2]. It’s a devastating process that involves pulmonary inflammation, alveolar damage and hypoxic respiratory failure. Recently, ARDS in adults was given a new definition under the Berlin definition, and is defined by acute hypoxemia, with bilateral infiltration on chest imaging that cannot be explained fully by cardiac failure or fluid overload [3]. There is no definition of ARDS in neonatal population.

The incidence of ARDS in the overall pediatric population is relatively low, with estimates ranging between 2.9 and 9.5 cases/100 000 children per year [2-4]. There is no incidence reported in the preterm infant, probably because ARDS is an entity not recognised in the neonatal intensive care unit (NICU) and possibly mis-classified as severe RDS or RDS not responding to surfactant.

In children, as well as in adults, the most frequent cause of ARDS is pneumonia, viral or bacterial systemic infection, major trauma or aspiration. Recent data suggest that up to 60% of very immature preterm infants may have been exposed to chorioamnionitis, and a proportion of them may be born with inflamed lungs or signs of fetal inflammatory response [5]. In stillborn fetuses exposed to chorioamnionitis, a pronounced pulmonary infiltration of inflammatory cells, an increased expression of proinflammatory cytokines and factors interfering with clearance of airway fluid have been identified. ‘Priming’ of the fetal lung by intrauterine proinflammatory cytokines and mediators is most likely a considerable factor in the initiation of the pulmonary pathogenetic sequence.

The two cases we present had acute severe foetal anemia with foetal sinusoidal rhythm and decreased foetal movement. There was no chorioamnionitis. Severe anemia as a cause of ARDS was not described in the adult and pediatric literature. The two preterm required 100% oxygen since birth, and did not respond to surfactant, Nitric oxide and high ventilation mean airway pressures. This could be suggestive that the lung insult began antenatally. Both our infants survived. Although the mortality of ARDS appears to be decreasing in clinical trials, several studies suggest that ARDS attributable mortality in children is lower than in adults (18–27%); however, data from Australia suggests that pediatric mortality from ARDS may be similar to adults (35%) [6]. There is no literature on ARDS treatment in preterm infants. The treatment in the NICU is the same as what is proposed for RDS. Surfactants, Positive pressure ventilation with supplemental oxygen are the cornerstones of therapy. Treating the primary cause (e.g., sepsis, pneumonia), minimizing the risk of multiple organ failure (MOF) and dysfunction and ventilator-induced lung injury (VILI) are essential [5].

Prone positioning has been proposed for improving oxygenation, respiratory mechanics, alveolar inflation and ventilation distribution, for homogenizing pleural pressure gradient and limiting lung over inflation. Prone positioning may be helpful in increasing lung volume, reducing the amount of atelectic lung areas in the dependent lung

and in facilitating the drainage of secretions [7]. Our first case was at 100% oxygen with high ventilation support. He was put on prone position and improved significantly with decreased FiO₂ to 60%. A Cochrane review showed that the prone position was significantly superior to the supine position in terms of oxygenation. Placing infants and children in the prone position may thus improve respiratory function. In this review, the benefits of prone positioning appear to be most relevant to infants because this age group has been more investigated. Among RTCs with >50 deaths in at least 1 treatment arm (n=21), 2 showed a statistically significant mortality benefit of the intervention (lower tidal volumes and prone positioning) [8]. Our two cases were put on HFOV after failure of conventional ventilation. HFOV has been proposed in the rescue treatment of ARDS when conventional ventilation has failed in infants and children. In adult patients, the interest in using HFOV could decrease in the wake of the publication of two recent multicenter, randomized trials. The first demonstrated that a HFOV strategy with high mean airway pressures led to more deaths than did a conventional mechanical ventilation strategy that used relatively high PEEP levels [9]. The second study did not find a major difference in outcome between HFOV and conventional mechanical ventilation [10]. There is at present insufficient data to confirm its advantages in the treatment of ARDS over conventional ventilation using a protective lung strategy. Our cases did not respond to surfactant treatment. Multiple surfactant abnormalities have been described in adult and child with ARDS. Surfactant deficiency in the premature newborn with RDS results from pneumocyte type II alveolar immaturity while ARDS in infants and children mainly develops from the impaired production and inactivation of surfactant. For these reasons, the preterm with ARDS is unresponsive to surfactant. It is unlikely that the use of surtanants as appropriate in premature infants (by bolus administration and in high doses) is the best modality for ARDS. An early, well-controlled trial of surfactant replacement therapy in adults concluded that the strategy had neither physiologic effect nor therapeutic benefit [11]. Other study, on the contrary, found that surfactant supplementation improves oxygenation and significantly decreases mortality in pediatric patients [12].

Both our cases were put on NO in the first hour after birth because severe unresponsive hypoxia and suspicion of PPHN which was confirmed secondarily by a cardiologist. In children with ARDS, a relatively large, double-blind, randomized, placebo-controlled trial was undertaken wherein oxygenation was the primary study endpoint. In this multicenter trial of 108 children, NO improved oxygenation at 12 and 24 h. However, by 72 h, there was no difference in oxygenation between the treatment and placebo groups [13]. Our infants responded to intravenous neumomucular blockers. This treatment is rarely used in neonatology. Neuromuscular blocking agents have been proposed as adjuvant therapy in ARDS, as they may decrease patient-ventilator asynchrony and, potentially, avoid the risk of barotrauma and biautma. In a multicenter, double-blind trial, 340 adult patients presenting to the intensive care unit (ICU) with an onset of severe ARDS within the previous 48 hours were randomly assigned to receive, for 48 hours, either cisatracurium besylate (a neuromuscular blocker) (178 patients) or placebo (162 patients). Mortality at 28 days was 23.7% (95% CI, 18.1 to 30.5) with cisatracurium and 33.3% (95% CI, 26.5 to 40.9) with placebo (P=0.05) [14].

Steroids are used for the second baby as a rescue treatment, but not for the first case. The use of steroids to decrease the inflammatory processes is theoretically justified but in the recent Pediatric Acute Lung Injury Consensus Conference, the resultant recommendation for steroids and ARDS was unequivocal and met the standard of strong agreement that at this time, corticosteroids cannot be recommended as routine therapy in pediatric ARDS [15].

Conclusion

We reported two cases where profound hypoxia persisted despite optimal treatment of classic RDS. They responded well to treatment know to be efficacious in pediatric and adult ARDS. A consensus definition, as well as criteria for the diagnosis of ARDS in the neonatal population is needed. A standard definition would allow comparisons with the broader ARDS literature, and possible studies on novel management strategies in neonates.

References