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■ Review article ■

Neonatal respiratory distress: recent progress in understanding pathogenesis and treatment outcomes

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= Abstract =

Transient tachypnea of the newborn (TTN), respiratory distress syndrome (RDS), and persistent pulmonary hypertension of the newborn (PPHN) are the three most common disorders that cause respiratory distress after birth. An understanding of the pathophysiology of these disorders and the development of effective therapeutic strategies is required to control these conditions. Here, recent papers on the pathogenesis and treatment of neonatal respiratory disease are reviewed. (Korean J Pediatr 2010;53:1-6)

Key Words : Transient tachypnea of the newborn, Respiratory distress syndrome, Persistent pulmonary hypertension of the newborn, Neonatal respiratory distress, Pathophysiology, Management

Introduction

Respiratory distress in newborn infants is common immediately after birth and is transient in most cases. However, when it persists, diagnostic procedures to determine the etiology and therapy are required to resolve the underlying problem. There are three common disorders that cause respiratory distress after birth: transient tachypnea of the newborn (TTN), respiratory distress syndrome (RDS) and persistent pulmonary hypertension of the newborn (PPHN). Here, I reviewed recent papers on the pathogenesis and treatment of these neonatal respiratory diseases.

Pathogenesis of disease

1. Transient tachypnea of the newborn (TTN)

TTN is a parenchymal lung disorder characterized by pulmonary edema that results from delayed resorption and clearance of fetal alveolar fluid in term infants[1]. The excess fluid in the lungs in TTN results in decreased pulmonary compliance and increased airway resistance. The mechanism causing changes in pulmonary function are primarily associated with the extrinsic compression of small airways by fluid in the extra-alveolar interstitium. Tachypnea develops to compensate for the increased work of breathing associated with reduced compliance and increased airway resistance[2].

2. Respiratory distress syndrome (RDS)

RDS is also known as hyaline membrane disease; it is the major cause of neonatal respiratory distress, especially in preterm infants. RDS is caused by a deficiency of surfactant. Surfactant is a phospholipid mixture that is responsible for stabilizing distal alveoli, at low end-expiratory lung volumes, by reducing surface tension[3]. When surfactant is deficient, the infant may not be able to generate the increased inspiratory pressure required to inflate alveolar units, resulting in the development of progressive atelectasis. Diffuse atelectasis results in low compliance, high resistance in small airways, and low functional residual capacity. Hypoxemia results primarily from mismatching of ventilation and perfusion as blood bypasses the atelectatic air spaces. Right-to-left shunting then occurs through the ductus arteriosus and foramen ovale because of increased pulmonary vascular resistance (PVR) and contributes to the decreased oxygenation[3, 4].

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3. Persistent pulmonary hypertension of the newborn (PPHN)

PPHN is caused by persistently elevated PVR that leads to right-to-left shunting through the foramen ovale and the ductus arteriosus, resulting in hypoxemia[5]. PPHN occurs primarily in term or late preterm infants (≥34 weeks of gestation). The high pulmonary resistance is caused secondary to a number of factors, including: low arteriolar and alveolar oxygen levels; hypercarbia; acidosis; alveolar fluid; lack of mechanical, rhythmic distention of the lung; and the net vasoconstricting humoral factors. Catecholamines, histamine, bradykinin, angiotensin, adenosine, serotonin, prostaglandins, thromboxane, atrial natriuretic peptide, endothelin, and nitric oxide (NO) are involved in the regulation of pulmonary vascular tone in the fetus[6]. Newborns with PPHN are at risk of severe asphyxia and its complications including death, neurologic injury and other problems. Studies over the past two decades have shown the critical role of NO-cyclic guanosilmonophosphate (NO-cGMP) signaling in the regulation of the fetal and neonatal pulmonary circulation, and that disruption of the NO-cGMP cascade during the perinatal period leads to PPHN[7].

Management of disease

1. Fluid restriction

Fluid restriction and metabolic monitoring are important factors of patient management. Urine output typically is reduced in infants with respiratory distress, even when the cardiac output is adequate. Excessive fluid increases the risk of patent ductus arteriosus, necrotizing enterocolitis (NEC), and bronchopulmonary dysplasia (BPD). Furthermore, morbidity and mortality have been observed to be lower in premature patients that were fluid restricted compared to preterm neonate in whom fluid intake was not restricted[8].

There is no evidence to support the routine use of diuretics in preterm infants with RDS. In addition, the administration of early nutrition is important in the overall care of these premature infants[9].

2. Transient tachypnea of the newborn

Because TTN is a benign, self-limited condition, patient management is primarily supportive. Supplemental oxygen is provided by hood or nasal cannula to maintain oxygen saturations above 90%. Infants with TTN rarely require more than 40% of FiO_2. However, if the required supplemental oxygen concentration is greater or the infant has an increase in the work of breathing as well as tachypnea, nasal continuous positive airway pressure (CPAP) is indicated[2, 10].

3. Respiratory distress syndrome

RDS is due to lung immaturity. The best intervention is to prevent premature birth. However, if premature birth cannot be avoided, RDS may be prevented with the use of antenatal steroid therapy and the prophylactic (early) administration of exogenous surfactant. Use of mechanical ventilation is associated with volutrauma and barotrauma, and the use of high concentrations of supplemental oxygen is associated with oxygen toxicity; all of which contribute to the development of BPD[11].

1) Steroid therapy

(1) Antenatal steroid therapy

Corticosteroids are given to the mother to help mature the lungs of the fetus before birth. There are different types of corticosteroids and they can be administered differently in various doses. Most trials have compared the two most commonly used corticosteroids before early birth, dexamethasone and betamethasone. Additional studies are needed to establish the best drug and method of delivery and the neonates in these trials need to be followed over a long period of time to monitor the effects on development[12].

(2) Postnatal corticosteroid therapy

The Committee on the Fetus and Newborn of the American Academy of Pediatrics does not recommend postnatal steroid administration. The use of late corticosteroids in babies that cannot be weaned from assisted ventilation (eg, an infant on maximal ventilatory and oxygen support), should be limited as well as the dose and duration of any course of treatment. Parents should be fully informed about the risks and agree to treatment[13].

2) Noninvasive mechanical ventilation

(1) Continuous positive airway pressure (CPAP)

Among premature infants without respiratory failure, CPAP is an alternative to mechanical ventilation to prevent atelectasis; this might help avoid the increased risk of BPD associated with mechanical ventilation[14]. Though the applicability of those results to current practice is difficult to assess (data of the 1970s), in larger babies with RDS, CPAP is associated with benefits in terms of reduced

respiratory failure and reduced mortality[15]. The potential benefit of CPAP compared to intubation and mechanical ventilation is less clear in infants born <30 weeks of gestation or with birth weights <1,500 g that have RDS[16].

(2) Neonatal nasal intermittent positive pressure ventilation (NIPPV)

NIPPV provides noninvasive respiratory support to premature infants that require endotracheal intubation and ventilation. It is uncertain whether the use of NIPPV is beneficial in neonates that require respiratory support and in what setting. NIPPV has been used for patients with apnea of prematurity following extubation. Further trials are required to delineate the role of NIPPV in the management of apnoea of prematurity[17].

3) Mechanical ventilation

(1) Pressure-limited (PL) ventilation

The most commonly used ventilator in neonates is the time-cycled pressure-limited (TCPL) continuous flow ventilator; the standard ventilator in the NICU for more than three decades. The delivered tidal volume is dependent upon the peak inspiratory pressure (PIP), the lung compliance and resistance, and the tube resistance. The TCPL ventilator is relatively simple to use and less costly than other ventilators. However, asynchrony has been associated with deterioration in oxygenation, increases in PCO_2, and reduction in tidal volume and minute ventilation. In addition, wide fluctuations in arterial pulse pressure during asynchrony may increase the risk of intraventricular hemorrhage[18].

(2) Synchronized and patient-triggered ventilation

Synchronized and patient-triggered ventilators are adaptations of the TPLC ventilatory system. They combine the features of the TPLC ventilator with a flow sensor at the airway opening of an endotracheal tube that detects changes in airway pressure, airflow, or respiratory movements as an indication of a spontaneous inspiration. The clinician sets the PIP, I:E ratio, respiratory rate, peak expiratory end pressure (PEEP), and FIO_2. With synchronized ventilation, when the sensors detect the onset of a spontaneous breath, the ventilator delivers an intermittent positive pressure breath at a fixed rate in synchrony with the infant's inspiratory effort, referred to as synchronized intermittent mandatory ventilation (SIMV)[19]. The overall mortality rate and incidence of BPD does not differ between infants that received synchronized versus non synchronized ventilation. The meta-analysis demonstrates that SIMV compared to CMV was associated with a shorter duration of ventilation (weighted mean difference −34.8 hours, 95% CI −62.1, −7.4)[19]. Evidence indicates that patient-triggered ventilation results in consistent tidal volume with a lower work of breathing, improves oxygenation especially in infants, >27 weeks gestation, shortens the duration of mechanical ventilation, decreases fluctuations in arterial blood pressure and decreases the proportion of infants on supplemental oxygen at 36 weeks postconceptional age[20].

(3) Pressure-support addition to SIMV

Pressure-support ventilation is a patient-triggered, pressure-limited, flow-cycled mode of ventilation. It delivers inspiratory support until the inspiratory flow decreases to a percentage of its peak value, usually 25%. Pressure support may be used with SIMV. During SIMV, only a predetermined number of the infant's breaths are supported by the ventilator, whereas during SIMV with pressure support all the infant's breaths are supported. Therefore, the addition of pressure support to SIMV compared to SIMV alone reduced the work of breathing as assessed by measurement of the pressure time product[21]. There are limited data comparing SIMV with pressure-support to SIMV alone. To date there have been no differences identified in the mortality rate, frequency of sepsis, patent duct arteriosus (PDA), grade III or IV intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), or stage III retinopathy of prematurity[21, 22].

(4) Volume-controlled (VC) ventilation

The clinician presets the tidal volume (generally 4 to 6 mL/kg), the respiratory rate, and an inspiratory time limit. The duration of inflation is dependent upon the time to deliver the set tidal volume. Recently a novel, randomised controlled trial of VC ventilation compared to PL ventilation in a population of preterm babies with RDS (G.A. 24-31 weeks, 600-1500 g) was reported. In this study, VC ventilation was found to be associated with faster weaning, reduction in duration of ventilation and improved survival, especially in the subgroup of babies weighing between 600 and 1000 g[23].

(5) Volume-guarantee (VG) ventilation

VG ventilation is a form of time-cycled, pressure-limited (TCPV) ventilation. An expiratory tidal volume, inspiratory time, and a maximum inspiratory pressure limit is selected. A flow sensor is placed on the endotracheal tube, which measures the inspired and expired tidal volume. The PIP varies up to the preset maximum pressure as the ventilator delivers the preset tidal volume. PIP decreases with improvement in lung compliance and increased spontaneous respiratory effort by the infant. Several studies have shown

that VG combined with either SIMV or patient-triggered PL ventilation compared to conventional PL ventilation, provided effective gas exchange while reducing the number of high volume mechanical breaths[24].

4) High frequency ventilation (HFV)

High frequency oscillatory ventilation (HFOV), a method of providing rapid ventilation with very small tidal volumes, appeared to be a promising alternative as it reduced lung injury in animal models compared to conventional ventilation. However, nearly all trials comparing HFOV to conventional ventilation performed in preterm infants with RDS (since surfactant replacement therapy has been available) have shown no increased benefit with regard to mortality and the development of BPD[25]. At present, there is no evidence that favors the routine use of HFV over conventional ventilation (CV). Nevertheless, when infants fail CV with persistent poor gas exchange and when PIP is $\geq$ 30 cm H_2O or the mean air pressure exceeds 12 cm H_2O in infants. HFV offers an alternate mode of ventilation that may provide better ventilation and oxygenation in the neonate with severe respiratory disease[26].

5) Inhaled nitric oxide (iNO)

It is well established that iNO provides benefit in the treatment of term or late preterm infants with persistent pulmonary hypertension. In a multicenter, randomized, controlled trial of inhaled nitric oxide therapy in premature newborns, early, low-dose inhaled nitric oxide did not reduce the risk of bronchopulmonary dysplasia in premature newborns with respiratory failure and a birth weight of 500 to 1250 g, but it did reduce the risk among infants with a birth weight of 1000 g or more[27]. A number of randomized controlled clinical trials have demonstrated that iNO did not increase the risk of short-term adverse events, particularly brain injury, and findings from one trial suggested that iNo may improve neurological outcomes in some premature infants[28]. However, the effective dose, duration, and time of administration of iNO are unknown. Based on currently available data, the routine administration of iNO to preterm infants with RDS is not recommended[29].

6) Surfactant therapy

A wide variety of surfactant preparations that include natural and synthetic products, have been developed. Currently, only natural surfactant preparations are available[30].

(1) Prophylactic surfactant therapy

Prophylactic surfactant is administered in the delivery room. Surfactant is administered from before the initiation of ventilation to up to 20 min. of life in infants at significant risk for RDS (i.e., those <30 weeks of gestation)[30, 31].

(2) Early surfactant therapy

Early surfactant therapy is administered during the first two hours of life frequently before the diagnosis of RDS is made[31].

(3) Rescue therapy

The rescue surfactant should be given when the diagnosis of RDS is established. The diagnosis is based on the infant's oxygen requirement, clinical examination, and chest radiographs[30-32].

With all three strategies, surfactant therapy improves mortality and morbidity in preterm infants when compared to untreated patients. However, clinical trials suggest that prophylactic or early therapy is superior to rescue therapy alone in infants at high-risk for RDS (<30 weeks gestation). In a meta-analysis, prophylactic administration of surfactant reduced the incidence of pneumothorax, pulmonary interstitial emphysema, and mortality when compared to the administration of surfactant for established RDS[32].

(4) Continued therapy

After the initial dose of surfactant is given for the treatment of RDS, the patient's response is assessed based on the continued oxygen requirements. Surfactant therapy is administered for a total of three to four doses based on the continued oxygen needs. Multiple doses of natural surfactants compared to a single dose leads to a lower frequency of pneumothorax and further reducing mortality rate[32, 33].

4. Persistent pulmonary hypertension of the newborn

Treatment strategies for PPHN are directed at reducing PVR. Mechanical ventilation is typically needed early during the course of PPHN. High-frequency ventilation or surfactant may be beneficial in infants with parenchymal lung disease. Cardiac output should be supported with pressors and fluid administration[5, 6].

1) Oxygen

Oxygen is a pulmonary vasodilator and initially should be administered in a concentration of 100% to infants with PPHN in an attempt to reverse pulmonary vasoconstriction. However, there is no advantage to maintaining an elevated PaO_2. Thus, the PaO_2 should be kept in the range of 50 to 90 mmHg (oxygen saturation >90 percent) to provide adequate tissue oxygenation and avoid lung injury that may result from continued administration of high concentrations of oxygen[6].

2) Assisted ventilation

Because hypercarbia and acidosis increase PVR, the goal is to establish and maintain normal ventilation ($PaCO_2$ 35 to 40 mmHg). When PPHN is associated with lung disease, atelectasis and the resulting maldistribution of ventilation may exacerbate high PVR. Assisted ventilation is used to recruit atelectatic segments, maintain adequate resting lung volume, and ensure appropriate oxygenation and ventilation[34]. Recent studies have shown that HFOV augments the response to iNO in PPHN associated with meconium aspiration syndrome or diffuse parenchymal lung disease (pneumonia, RDS)[35].

3) Surfactant

In a randomized trial of term infants with severe respiratory failure, surfactant administration significantly reduces the need for extracorporeal membrane oxygenation (ECMO) therapy (29 versus 40% with placebo), without increasing the risk of complications. However, there appears to be no effect when PPHN was the primary diagnosis (30 versus 32%)[36].

4) Inhaled nitric oxide (iNO)

Endogenous NO regulates vascular tone by causing relaxation of vascular smooth muscle. When inhaled, NO is a selective pulmonary vasodilator. Inhaled NO improves oxygenation and reduces the need for ECMO in term and late preterm infants with severe PPHN and does not appear to have toxicity[37]. In a a multicenter, randomized trial, early initiation of iNO with low-dose, did not reduce the overall incidence of bronchopulmonary dysplasia, except among infants with a birth weight of at least 1000 g, but it did reduce the overall risk of brain injury[38]. It also did affect the outcomes of neurodevelopment and hearing among the surviving infants evaluated at two years of age[39].

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