Chapter

Neonatal Respiratory Distress Syndrome: Things to Consider and Ways to Manage

Bita Najafian and Mohammad Hossein Khosravi

Abstract

Involving more commonly the premature (less than 37 weeks of gestational age) infants, neonatal respiratory distress syndrome is an important clinical syndrome responsible for a high rate of mortality and morbidity. The main progress in respiratory distress syndrome (RDS) management is attributable to prescription of surfactant for fastening pulmonary maturation. Respiratory protection, such as mechanical ventilation and nasal continuous positive airway pressure, and surfactant are building blocks of disease treatment. In this chapter, we are going to have a rapid review on epidemiology, diagnosis and treatments of RDS.

Keywords: respiratory distress syndrome, epidemiology, treatment, etiology

1. Introduction

Involving more commonly the premature (less than 37 weeks of gestational age) infants, neonatal respiratory distress syndrome (NRDS), is an important clinical syndrome responsible for a high rate of mortality and morbidity. Reports have shown that about 12% of infants are preterm in the United States, while the prevalence ranges between 6 and 11% in European countries [1, 2]. NRDS is a leading cause of admission to neonatal intensive care unit (NICU) with estimated incidence rate of 7.8% and mortality rate of 50% in premature infants [3–5]. The severity usually increases during the first 48 hours of birth [6]. The prevalence and the severity of NRDS decrease as the gestational age increases [7–9].

A variety of factors including cesarean section, prematurity, maternal diabetes and genetic variations have been reported to play role in pathogenesis of NRDS [10, 11]. Damage to type II alveolar cells is another considered mechanism for NRDS. Diffuse alveolar capillary injury results in progressive increased permeability as well as pulmonary and alveolar edema, which make the type II alveolar cells nonfunctional. All these processes lead into severe hypoxemia due to abnormal ventilation/perfusion ratio [12, 13].

NRDS is a result of pulmonary immaturity mostly caused by insufficient levels of surfactant [14, 15]. The condition is developed through hypoventilation, hypoxemia and respiratory acidosis [14, 15].

2. Diagnosis

Early diagnosis is of a high importance due to available management methods [15, 16]. A combination of clinical signs and different modalities such as chest radiographies and laboratory tests are needed for diagnosing NRDS [14].

2.1 Clinical signs and symptoms

There are a wide range of clinical signs from nasal flaring and cyanosis to substernal and intercostal retraction, tachypnea and grunting [16]. A risk assessment tool called "Clinical Risk Index for Babies" (CRIB) is used to estimate the need for admission of infants in NICU [17]. Different factors such as gestational age, birth weight and base excess during the first 12 hours of life, fraction of inspired oxygen and presence of congenital malformations are considered in this assessment (**Table 1**).

2.2 Laboratory tests

Arterial oxygen pressure (PaO_2) is a marker for diagnosis of NRDS. PaO_2 less than 50 mmHg with cyanosis in room air or need for supplementary oxygen for maintaining O_2 level above 50 mmHg are indicators for NRDS [14]. Metabolic and respiratory acidosis are measured through a blood sample.

Gastric aspirate shake test (GAST) is another laboratory measure with reported sensitivity of 100% and specificity of 92% for diagnosis of NRDS [18]. GAST identifies presence or lack of surfactant in the gastric fluid aspirates [19].

Recently published studies have mentioned a new factor for early detection and prediction of NRDS in premature infants. Transforming growth factor β1 (TGF-β1) is a cytokine, which has the responsibility for regulating and differentiating different cell lines [20, 21]. These studies have marked the role of TGF-β1 in development of various acute and chronic lung injuries and concluded that this factor can be used as a diagnostic and prognostic one [22]. The same role has been considered for interleukin-6, which is a glycoprotein secreted mostly from T cells and mononuclear macrophages causing inflammatory reactions [23, 24].

2.3 Chest radiographs

Previous studies have reported a remarkable diagnostic value for chest radiographs [25]. Features such as reduced lung expansions, air bronchograms and dilated bronchioles can be seen in NRDS [15]. In addition to diagnostic use, chest radiographs have another application to confirm endotracheal tube position. Premature infants receive continuous positive airways pressure (CPAP) for augmenting oxygenation in addition to simplifying intra-tracheal administration of surfactants [14]. The precise adverse effects of radiation have not been yet determined; however, some efforts are being done to find an alternative method for chest radiography [26–28].

2.4 Ultrasound

Previously, lung ultrasound (LUS) was not used for infant chest imaging due to interference of air levels. This modality has its own potential adverse effects including thermal and mechanical tissue damage [27, 29]. Recently, lung ultrasound

Factor	Score
Birth weight (gr)	
>1350	0
851–1350	1
701–850	4
≤700	7
Gestation (week)	
>24	0
≤24	1
Congenital malformations*	
None	0
Not actually life-threatening	1
Actually life threatening	3
Maximum base excess in first 12 h (nmol/L)	
>−7	0
−7 to −9.9	1
−10 to 14.9	2
≤−15	3
Minimum appropriate FIO_2 in first 12 h	
≤40%	0
41–60%	2
61–90%	3
91–100%	4
Maximum appropriate FIO_2 in first 12 h	
<40%	0
41–80%	1
81–90%	3
91–100%	5

**Excluding inevitably lethal malformations.*

Table 1.
CRIB score.

has been widely used as an accurate diagnostic tool according to published clinical studies [4, 7, 16, 30–34]. Lack of normal air-filled levels and presence of fluid level is a diagnostic clue for NRDS.

A meta-analysis of six studies comparing LUS to chest x-ray for diagnosing NRDS reported a high diagnostic sensitivity (97%) and specificity (91%) for LUS [35]. They have also reported that transthoracic technique is superior to transabdominal approach for diagnosing NRDS.

On the other hand, some researchers believe that lung ultrasound can be helpful only as a complementary diagnostic tool rather than a diagnostic method [36]. They have mentioned in a letter-to-editor that only chest radiographs and CT scan can be reliable for diagnosing neonatal respiratory distress syndrome.

3. Management

3.1 Mechanical ventilation

Mechanical ventilation is the most commonly applied treatment method for NRDS in clinical practice [37–39]; although mechanical ventilation and continuous oxygen therapy are independent risk factors for development of NRDS to bronchopulmonary dysplasia (BPD) [40, 41]. Noninvasive respiratory support methods such as nasal intermittent positive pressure ventilation (NIPPV), high flow nasal cannula (HFNC) and nasal continuous positive airway pressure (NCPAP) are being used more commonly as the initial ways of management, which may decrease need for intubation in up to 50% of infants [42–44]. On the other hand, the failure of noninvasive respiratory support results in delayed administration of surfactant and prolonged mechanical ventilation. Also, this may be associated with higher incidence of bronchopulmonary dysplasia (BPD), major morbidity or even death [45, 46]. So, it seems that a combination of early respiratory support and prescription of surfactant may improve the treatment results. Administration of surfactant during NCPAP, less-invasive (LISA) and minimal-invasive surfactant administration (MISA) have shown convenient results in management of NRDS [47].

Recently published studies have introduced the aerosolized surfactant as a safe and efficient method of drug delivery [47]. It has been claimed that vibrating and ultrasonic mesh nebulizers have the ability to make surfactant aerosols without interfering with biochemical composition of medication [48–50]. It has been reported that aerosolized surfactant can be delivered using nasal cannula in noninvasive respiratory support [51–55].

3.2 Surfactant

Pathophysiology of NRDS (inadequate production of pulmonary surfactant in premature infants) was first discovered by Avery and Mead in 1959, which resulted in changing the former name of the disease "hyaline membrane disease" [56]. This was a window to surfactant replacement therapy.

Lung surfactant is a mixture of phospholipids and some specific proteins secreted by epithelium of alveoli, which lines the small airways. It primarily reduces the surface tension of liquid presented in terminal air spaces [57]. Lack of pulmonary surfactant is the main result of NRDS; so, prescription of pulmonary surfactant can augment respiratory function and pulmonary compliance resulting in elevated oxyhemoglobin level [58–61]. Lack of surfactant results in a chain of problems from collapsed lung, tissue damage, reduced oxygenation and impaired function of alveolar epithelium, resulting in altered production of surfactant [62]. Fujiwara et al. reported the very first application of surfactant-TA in preterm infants with respiratory distress syndrome in 1980 [63].

There are different kinds of animal-derived as well as first- and second-generation synthetic surfactants [64]. As a natural surfactant, Curosurf is taken from pig lung, which is consisted of 41–48% lecithin and 51–58% of hydrophobin and other phospholipids. Liquid gel layer has the responsibility to absorb the Curosurf after its administration to the lungs [65]. Also, this medication has some adverse effects including respiratory discomforts and bucking [66, 67]. Administration of surfactant involves frequent endotracheal intubation (INSURE: INtubation-SURfactant-Extubation) and mechanical ventilation, which is associated with inevitable comorbidities [68, 69].

Recently, in addition to the common INSURE method, a new method has come up and is getting more popular. This method is called a less-invasive surfactant administration (LISA), which has been reported to be more effective in prevention of bronchopulmonary dysplasia and reducing preterm infants' mortality. In this method, surfactant is delivered through a thin catheter while the infant is under continuous positive airway pressure (CPAP) treatment. However, more large-scale randomized clinical trials are needed to make this method accepted as a routine in clinical practice [70].

3.3 Ambroxol hydrochloride

As an active metabolite of bromhexine, ambrotherxol or ambroxol hydrochloride has a mucolytic activity. A wide range of advantages have been reported for ambroxol hydrochloride from reducing production of hydrogen peroxide, stimulating secretion of pulmonary surfactant, reducing lung damage and alleviating the inflammatory response to relieving pulmonary edema and interstitial exudation. As a low-cost and high-efficacy medication, ambroxol hydrochloride is being used in clinical treatment of NRDS [71, 72]. There are reports about satisfactory results of combination of high-dose ambroxol hydrochloride and surfactant [37].

3.3.1 Nitric oxide (NO)

About 2% of all live births are involved with respiratory failure, which is responsible for more than one-third of neonatal mortalities [73]. Inhaled NO (iNO) reduces pulmonary vascular resistance, edema, lung inflammation and hypoxia, which makes the respiratory difficulties easier for infants [74]. Previous researches have also shown that iNO improves pulmonary angiogenesis and protects pulmonary system against infections with no remarkable adverse effects on growth or neurodevelopmental status [75].

Neonatal respiratory distress syndrome (NRDS), as a result of inadequate surfactant production, leads to atelectasis and ventilation-perfusion (V/Q) mismatching. Beside notable response to exogenous surfactant, it has been reported that iNO transiently improves oxygenation in infants with NRDS. Previous studies have shown that iNO therapy alone reduces mortality rate in preterm infants [76]. iNO improves V/Q matching, selectively dilates the pulmonary vasculature and decreases pulmonary inflammatory response. The most convenient advantage of iNO is reducing incidence of chronic lung disease in premature infants with RDS [77]. In other researches, premature infants with suboptimal response to exogenous surfactant showed beneficial clinical responses to combination therapy with iNO [78].

4. Prognosis

Neonatal respiratory distress syndrome is one of the major causes of premature death; however, a notable part of the survivors may develop bronchopulmonary dysplasia and suffer from chronic pulmonary diseases [67]. Prognosis of RDS is highly related to the treatment and management methods, which have been being developed since their discovery. The efficacy of each method for prognosis is under investigation. Also, gestational age has an important role in determining the prognosis, where late preterm infants usually have a better prognosis in comparison with early preterm infants.

5. Conclusion

According to high prevalence and clinical importance of NRDS, seeking new methods of diagnosis and treatment is of a high importance. Available knowledge approves efficacy of surfactant as the stumbling block of medical NRDS management; however, various methods of drug delivery are under development. It seems that a combination of respiratory support and surfactant is the ideal method of management.

Conflict of interest

There are no conflict of interests in terms of the present chapter.

Author details

Bita Najafian[1*] and Mohammad Hossein Khosravi[2]

1 Department of Pediatrics, Faculty of Medicine, Baqiyatallah University of Medical Sciences, Tehran, Iran

2 International Otorhinolaryngology Research Association (IORA), Universal Scientific Education and Research Network (USERN), Tehran, Iran

*Address all correspondence to: dr.najafian@yahoo.com

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