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Review Article

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Neonatal Respiratory Distress Syndrome in a Nutshell

Akumtoshi

Department of Pediatrics, Zion hospital and research centre, Dimapur, India

***Corresponding author**
Akumtoshi, Department of Pediatrics, Zion hospital and research centre, Dimapur, India. Tel: +91-8974439288; Email: akumtoshi@gmail.com

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Abstract

Respiratory distress syndrome (RDS) is an important cause of mortality and morbidity in preterm neonates. With the increasing number of preterm deliveries globally according to the World Health Organization, it is imperative to consider a safe place for delivery and a good obstetric care to start with. Antenatal steroids are helpful not only in reducing the risk of RDS but also reducing necrotizing enterocolitis (NEC) and Intraventricular hemorrhage which further improves the outcome of a preterm delivery. Delayed cord clamping is recommended as it reduces mortality in preterm newborns. Use of optimal oxygen and getting CPAP into the delivery room has improved the outcome and reduced the need of mechanical ventilation thus reducing the risk of Chronic Lung Disease (CLD). Timing the administration of surfactant is important to avoid mechanical ventilation. The increasing use of non-invasive ventilation has reduced ventilator induced lung injury and CLD. Many have embraced Heated Humidified High Flow Nasal Oxygen (HHHFNC) as an alternative to CPAP and its use has increased in view of its ease of use and lesser trauma. Caffeine facilitates early extubation in intubated preemies on ventilators and improves neurodevelopment outcome. Adequate nutrition and proper temperature control starting from the point of delivery cannot be emphasized enough for this group of population.

Neonatal respiratory distress syndrome (RDS) previously also known as hyaline membrane disease (HMD) is an important cause of mortality and morbidity in preterm neonates. Preterm deliveries are increasing globally according to the World Health Organization and they need special care by well trained personnel in well equipped centres.

Respiratory distress syndrome (RDS) is a disease affecting preterm infants, caused by insufficient pulmonary surfactant. Apart from prematurity, the incidence of RDS have been seen to be higher in male infants, babies born to mother with diabetes, infants with mutations in surfactant proteins and cesarean deliveries [1]. Infants of African origin/ancestry are at lower risk for developing RDS due to their protective genetic polymorphism. These babies are born before 37 weeks of gestation when the lungs are still developing and usually in the saccular or canalicular stage of fetal lung development [1, 2].

It was president JF kennedy's son, Patrick Kennedy, who was born prematurely at almost 37 weeks of gestation, and died after 39 hours of life on Aug 7, 1963 due to RDS. This unfortunate event sparked many researches towards the survival of preemies and probably increased funding for research by the National Institutes of Health [3].

Initially it was Kurt von Neergaard in 1929 a Swiss physician who suggested the presence of surfactant and its relevance to the newborn's first breath but it was rather ignored for a long time. 20-25 years later, Richard Pattle, John Clements and Chris Macklin, contributed to the understanding of pulmonary surfactant. Later in 1959 Mary Ellen Avery and Jere Mead published evidence that RDS had a deficiency of pulmonary surfactant [4].

Surfactant is identifiable in fetal lung as early as 16 weeks, though its proper secretion begins after 24 weeks and by 36 weeks surfactant is sufficiently produced. However, by 24 weeks of gestational age the lungs have sufficient surface area to meet oxygen requirement for an ELBW but type II alveolar cells are less & cannot produce enough surfactant to avoid RDS [1].

Pulmonary surfactant is a complex mixture of phospholipids (PL) and proteins (SP) that reduces surface tension at the air-liquid interface of the alveolus, thus preventing its collapse during end-expiration. It mostly consist of phospholipids (80%) mainly dipalmitoylphosphatidylcholine (DPPC), 10% consist of surfactant protein (SP-A, B, C and D) and the remaining 10% consist of neutral lipids, mainly cholesterol. Absence or diminished surfactant results in reduced lung compliance from 1-2 ml/cmH_2O/kg to 0.2 -0.5 ml/cmH_2O/kg, which causes progressive atelectasis, loss of functional residual capacity (FRC) from 30 ml/kg to as low as 4- 5 ml/kg and finally ventilation perfusion mismatch [5, 6].

According to the Vermont Oxford Network in 2017, at 28 weeks' gestation RDS was about 80%, and as high as 90% at 24 weeks' gestation. Crowley and colleagues in 1990 published a meta-analysis of 12 randomized controlled trials of antenatal corticosteroids, demonstrating that this therapy significantly reduced RDS and other neonatal morbidities such as intraventricular hemorrhage (IVH) and necrotizing enterocolitis (NEC) as well as overall neonatal mortality

[7]. The American College of Obstetricians and Gynecologists recommends a course of corticosteroids for pregnant women between 24 0/7 weeks and 33 6/7 weeks of gestation who are at risk of preterm delivery within 7 days, including for those with ruptured membranes and multiple gestations. [8, 9].

As much as feasible, extremely preterm babies should be transported in-utero if possible to tertiary centers where appropriately skilled healthcare givers are available and where there is a high throughput of VLBW babies which improves the rate of survival. Magnesium sulphate ($MgSO_4$) should be given to mothers with imminent preterm delivery which helps reduces cerebral palsy at 2 years of age by about 30% [10]. Cord clamping should be delayed by at least 60 seconds to improve outcome of preterm deliveries; it also helps in better transition from fetal to neonatal life according to the Australian Placental Transfusion Study (APTS) [11]. Maintain a warm delivery room of about 26 Celsius. Fio_2 if required is given at 30% in <28 weeks of gestation, for 28-31weeks gestation Fio_2 of 21-30% is used and in >32 weeks gestational age 21% Fio_2 is used [12, 13]. The aim is to achieve an SpO_2 of 80% or more by the end of 5 minutes in order to reduce mortality and intracranial hemorrhage. Once stable, Spo_2 of 90-94% is maintained [14].

Spontaneously breathing babies are started on CPAP rather than intubated, if respiratory support is needed in the delivery room to reduce the risk of Bronchopulmonary dysplasia (BPD). If RDS develops, infants will present with tachypnea in order to maintain their minute ventilation, chest retraction due to the highly compliant chest wall, flaring of the alae nasi as they are obligate nasal breathers –in order to increase the air flow, grunting in order to prevent alveolar collapse and Cyanosis [15]. The severity of respiratory distress is assessed by Silverman-Anderson Score and Downes' Score [1]. While the Silverman Anderson Score is more suited for preterms with HMD, the Downes' Score is more comprehensive and can be applied to any gestational age and condition. Chest radiograph in RDS should be done and is characterized by a diffuse reticulogranular pattern and hypoexpansion depending on the degree of severity [16, 17].

For diagnosing RDS the Neonatal-Perinatal Database (WHO)-South East Asia, requires all of the following three criteria:

- Preterm neonate.
- Respiratory distress having onset within 6 hours of birth.
- Amniotic fluid L/S ratio of <1.5, or negative gastric aspirate shake test, or X ray evidence.

All of the three criteria or an autopsy evidence of HMD [18].

Cardiac anomalies need to be excluded by doing an echocardiogram, and exclude sepsis and pneumonia.
The SUPPORT trail supports the consideration of CPAP instead of intubation and surfactant in preterm babies which helps reduce the risk of BPD. Prophylactic surfactant, which is giving surfactant to preterm babies within the first 30 minutes of birth, is avoided as it is associated with higher incidence of BPD and death compared with CPAP. To provide measurable CPAP from birth, T-piece device is a better choice than a self-inflating anesthetic bag [19]. Surfactant is indicated if intubation is required during stabilization and early rescue surfactant (within 2 hours of birth) is given if signs of RDS develop [20]. For babies already on CPAP, surfactant is given if Fio_2 requirement goes more than 30% with a PEEP of 6 or more. IN-SUR-E technique has been widely used successfully, but studies suggest that less invasive surfactant administration (LISA) is superior in terms of reducing the need for mechanical ventilation (MV) and the combined outcome of death or BPD [21]. LISA is a method by which surfactant is directly placed into the trachea using a fine catheter under direct or video laryngoscopy [22].

There are different sources of surfactant and there have been some head-to-head trials which show that different surfactants have similar efficacy when used in similar doses; however, there is an advantage of survival when 200 mg/kg of poractantalfa is compared with 100 mg/kg of beractant or 100 mg/kg poractantalfa to treat RDS. Bolus administration of surfactant as compared to infusion has a more uniform distribution in the lungs and lesser incidence of reflux [23]. A repeat dose of a maximum of 3 and rarely 4 doses are required. Laryngeal mask airway can also be used to administer surfactant but the unavailability of smaller sizes is its limitation [24]. Pharyngeal deposition of surfactants and nebulization methods are under trail. Synthetic surfactants having both SP-B and SP-C analogues are also currently under clinical trials [1].

At the moment, there is no clarity on whether to sedate routinely for LISA or not, and one must decide for themselves, although there are evidence of CPAP failure following sedation. One must be watchful after giving surfactant to see for pulmonary hemorrhage although rare [25]. If the baby was already on mechanical ventilator, make sure to reduce the pressures unless the baby is on volume targeted mode, to avoid barotraumas after administering surfactant.

The basic principle of treating RDS is to keep the alveoli open for adequate oxygenation and ventilation. CPAP is one such device that causes splinting of the airway, thus maintaining lung expansion (functional residual capacity) and preventing alveolar collapse during end-expiration. It also helps recruit collapsed alveoli even in the absence of surfactant [1]. CPAP is now recommended as the optimal first mode of respiratory support in RDS. The gas in CPAP has to be delivered heated and humidified, with a measurable and controllable pressure. CPAP is indicated at birth in all babies at risk of RDS (in < 30 weeks GA) who do not need intubation for stabilization. CPAP with early rescue surfactant is considered optimal for babies with respiratory distress or RDS. The preferred interface is short binasal prongs or nasal mask. CPAP is initiated with a PEEP of 5 to 6 cm H_2O pressure and adjusted to an optimal PEEP based on chest x-ray with 8 to 9 rib expansion [18]. With Optimal PEEP, Fio2 requirement reduces to less than 30%, and this is when we can start weaning the CPAP by reducing the PEEP by 1 cm of H_2O each [1]. For preterm >32 weeks gestational age, we can discontinue CPAP at PEEP 5 and Fio_2 <25%, but for <32 weeks gestational age, poor chest wall compliance can lead to atelectasis, therefore longer use of low CPAP or a more gradual weaning may be advantageous, even when no oxygen is needed [1].

CPAP failure is Defined as the need for intubation or escalation to higher respiratory support (NIPPV/MV) due to persistence of severe respiratory distress and the need for a high FiO_2 >40% despite PEEP of 6 cm H_2O. This is when mechanical ventilator becomes useful [26]. The preferred mode of ventilation is Volume targeted ventilation (VTV) as it helps in automatic weaning after surfactant is administered [1].

HIPSTER trial compared HFNC with CPAP as a primary mode of support in the delivery room for infants > 28 weeks, but was

stopped early because more infants started on HFNC needed rescue CPAP. HFNC can be useful during weaning from CPAP once Fio_2 requirement is <30% and has an advantage of lesser nasal trauma compared to CPAP. Although widely used, there is no evidence that BIPAP is advantageous over CPAP. Synchronised NIPPV (nasal intermittent positive pressure ventilation), if delivered through a ventilator rather than BIPAP device, can reduce extubation failure, but has no advantage in reducing BPD. High frequency oscillatory ventilator (HFOV) vs conventional MV show modest reductions in BPD with HFOV, although there is less trials where volume targeting is used with MV [18]. Neurally adjusted ventilator assistance (NAVA) ventilation offers better synchronisation as it uses electrical impulse from the diaphragm as trigger, but further research is required. Nasal HFOV has also been tried but the benefits are still inconclusive. Extubation from MV is tried as soon as possible, as long as the baby is clinically stable. We can extubate once the MAP is 8 on conventional ventilator and 9 on HFOV. They can be stepped down to nCPAP and gradually weaned [27].

PHELBI trial suggest to allow moderate hypercarbia ($PaCO_2$ of 60mmHg/8kPa) during weaning provided the pH remains above 7.22, but higher than 60mmHg can actually worsen outcome and is avoided. Caffeine for Apnea of Prematurity (CAP) study showed Caffeine facilitated earlier extubation with reduction in BPD and better neurodevelopmental outcomes at 18 months [28]. Caffeine is given in all infants <1,250 gram birth weight soon after birth. In infants >1,250 gram birth weight who require ventilation, we begin caffeine prior to extubation. Inhaled budesonide (IB) can be considered in infants at very high risk of BPD [29]. NEUROSIS trial although showed reduced (PDA) persistent ductusarteriosus and BPD following IB, but there was a trend of *increased mortality* with IB. Short tapering course of low dose dexamethasone can be considered to facilitate extubation who remain on MV for 1–2 weeks [30].

Supportive care cannot be taken lightly in preterm newborns with RDS. Maintain body temperature of 36.5-37.5 Celsius, humidity of 60-80%, start enteral feed on day one if hemodymanically stable and fluids (restricted regimen) & nutritional support (TPN) is to be started on day one itself. Defining hypotension as a mean arterial pressure less than gestational age in weeks is widely accepted. Proper monitoring of the patient is essential by all means [31, 32].

Abbreviations

VLBW = very low birth weight
ELBW = extremely low birth weight
BPD = bronchopulmonary dysplasia
TPN = total parenteral nutrition

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