The Utilization of Exogenous Surfactant in the Neonate

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Abstract

Respiratory distress syndrome (RDS) is a common consequence of pulmonary immaturity in the lungs of neonates. RDS is the result of the deficient secretion of endogenous surfactant, causing increased surface tension in the alveolar sacs leading to respiratory compromise. RDS is more common in the preterm neonate but can be experienced by neonates at any gestational age. Treatment for RDS formerly consisted of mechanical ventilation and oxygen therapy to treat and relieve symptoms but not the cause. A new treatment method, developed largely in the 1980s and 90s is the use of exogenous surfactant to treat the deficiency exhibited in RDS. The administration of exogenous (natural or artificial) surfactant has been shown to greatly decrease the rate of respiratory failure in neonates experiencing respiratory distress and has greatly increased their survival rate. The current use of exogenous surfactant in neonates with RDS has greatly reduced the morbidity and mortality rates of neonates suffering from this disease.

The Utilization of Exogenous Surfactant in the Neonate

Respiratory distress syndrome (RDS) is a disease observed in neonates that is caused to pulmonary immaturity. It is caused by the lack of an endogenous substance, called surfactant, normally produced by the lungs. This substance is responsible for facilitating and maintaining inflation of the lower airways and diffusion of oxygen into the pulmonary capillaries. Without it, breathing is nearly impossible and symptoms such as accessory muscle use, cyanosis, and tachypnea ensue rapidly after birth. Former treatment methods consisted mostly of the use of mechanical ventilation and oxygen therapy; today however, treatment involves the administration of an exogenous form of surfactant. The development of exogenous surfactant therapy has decreased the morbidity and mortality rates of neonates with RDS immensely; because of its institution in most neonatal care environments, RDS is rarely manifested in otherwise healthy neonates beyond their first few hours of life (Wrobel, 2004).

Hyaline Membrane Disease

In the early 1950-1960s, a respiratory disorder, hyaline membrane disease, was affecting tens of thousands of premature and full term neonates each year. With its pathophysiology not yet fully understood by clinicians, treatment options were minimal and nonspecific. The most prominent victim of this disease was the son of President John F. Kennedy and First Lady Jacquelyn Kennedy who expired two days after he was born five and a half weeks prematurely (Wrobel, 2004). It was at this time that physicians and scientists started working together to uncover the mystery of this unidentified neonatal killer.

Respiratory Distress Syndrome

Discovery of the Disease

The disease formerly known as hyaline membrane disease is now commonly referred to as RDS. The original name of this mysterious disease was derived from the hyaline membranes found at autopsy in the lungs of neonates whose cause of death was unknown. Most physicians believed these membranes were the culprits of many premature infant deaths. However, their origin was unclear. Some speculated that the membranes were formed from neonates aspirating amniotic fluid or milk. Regardless of how they formed or where they came from, it was believed that the membranes themselves impeded airflow, causing the symptoms observed in many neonates, including circumoral cyanosis, dyspnea, retractions, and grunting (Wrobel, 2004).

One of the major turning points in the investigation of this neonatal disease was when pathology studies revealed the presence of fibrinogen, a protein normally found in the blood, composed among the hyaline membranes. This revealed that the membranes must have formed within the infant's own body, rather than an extrinsic source. This discovery shifted the research focus to the internal composition of the neonatal respiratory tract. Another advancement was made in the study of this disease when researchers found that only infants who had taken at least a few breaths displayed these hyaline membranes, and such structures were never observed in the lungs of stillborn infants. This suggested that the membranes were formed endogenously in the lungs as a result of lung injury rather than the cause of injury (Wrobel, 2004).

Dr. Mary Ellen Avery, a pediatric resident at Johns Hopkins in the mid-1950s, was a pioneer of research on hyaline membrane disease. She had observed many

neonates experience the same struggle to breathe and wondered what was really causing this terrible disease. One discovery she uncovered was that unlike babies who died of other causes, those who died of hyaline membrane disease had no residual air in their lungs at autopsy (Wrobel, 2004). Dr. Avery found it hard to understand this finding because it did not make sense that these babies whom she watched struggle for breath seemed to be unable to retain air.

This question ultimately led Dr. Avery and her colleague Dr. Jere Mead to discover the mechanism underlying the inability of these premature infant lungs to expand and retain air. An earlier discovery by physiologist John Clements of a substance called surfactant led Avery and Mead to conclude that hyaline membrane disease was not caused by the presence of something foreign but rather the absence of something intrinsic: endogenous surfactant (Wrobel, 2004). Surfactant lines the alveoli in the lungs, which are the small air sacs responsible for perfusion and oxygen delivery to the blood (Davidson, London, & Ladewig, 2012). The discovery of surfactant explained why the disease primarily affected premature neonates, whose lungs were not yet able to produce surfactant, as sufficiently as full-term neonates. It also explained why not only breathing in required extra effort, but expiration did as well, leading to the infant's inability to retain air. Without this substance, the surface tension of the alveoli was too high, making the air spaces too unstable, causing their collapse. This major discovery on the cause of respiratory distress exhibited in neonates led to a shift in research and treatment options, ultimately leading to the production and utilization of exogenous surfactant as the primary method of treatment.

Normal Neonatal Pulmonary and Surfactant Development

A pregnancy is considered to be full term at 40 weeks gestation. Infants born before 37 completed weeks are considered preterm. Preterm infants are at a higher risk for certain problems of immaturity, including RDS, low birth weight, jaundice, retinopathy of prematurity, and heart murmurs among other disorders related to underdevelopment. The first few hours of life, known as the neonatal transition period, is a critical time for the identification and treatment of various cardiovascular and respiratory abnormalities, where rapid intervention may be necessary. During the newborn period, which is the time from birth through the twenty-eighth day of life, the newborn undergoes numerous physiologic adaptations in order to make the successful transition from intrauterine to extrauterine life. One of the major adaptations a newborn must undergo is an adaptation of the respiratory system (Davidson et al., 2012).

The respiratory system is composed of an upper and lower respiratory tract. The upper airway consists of the nose, mouth, pharynx, epiglottis, larynx, and trachea and facilitates airflow. When air enters the respiratory tract through the nose, it is warmed, moistened, and filtered by the nasal mucosa. From there it enters the pharynx, located in the back of the mouth, commonly called the throat. The pharynx terminates at the epiglottis, which protects the entrance to the larynx leading to the trachea. The epiglottis covers the larynx during swallowing to prevent aspiration and opens to allow the passage of air. Beyond the trachea is the beginning of the lower respiratory tract, which consists of the bronchi, bronchioles, alveolar ducts, and alveoli. The lower respiratory tract is responsible for perfusion. The lower airway, with the exception of the bronchi, is located

entirely inside the lung tissue. The main stem bronchi subdivide into smaller bronchioles, leading to the alveolar ducts and terminating at the alveoli.

The alveoli are small grape-like clusters of air sacs, which are the primary site of gas exchange (Grossman, 2014). Gas exchange occurs at the alveolar-capillary membrane where the alveoli are in contact with pulmonary capillaries and transfer oxygen and carbon dioxide by diffusion across the membrane. Alveoli have the natural tendency to collapse, as they are very unstable. In order to keep these tiny air sacs open, the alveoli secret the lipoprotein surfactant to create the necessary surface tension to keep the alveoli patent (Eisel, 2014). Figure 1 below illustrates the human respiratory anatomy.

Figure 1. The Human Respiratory Anatomy

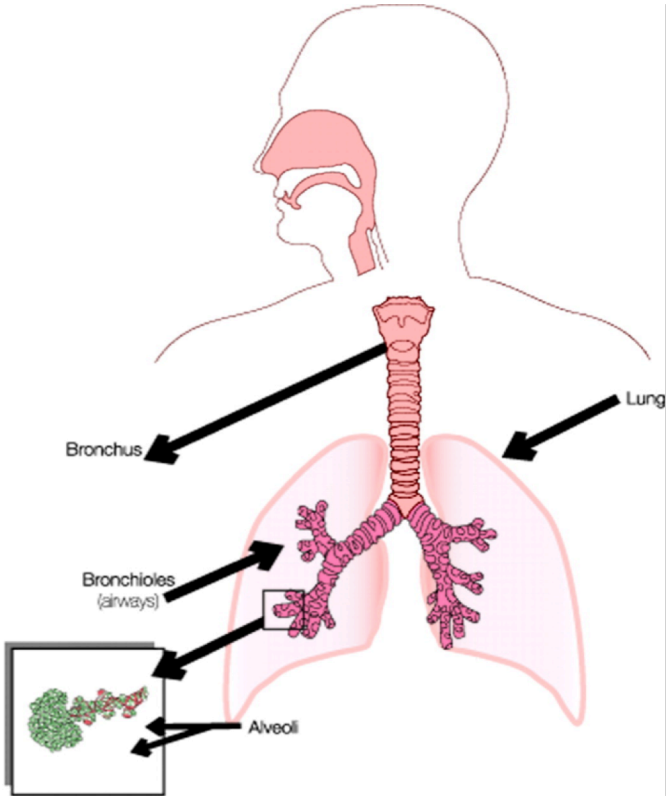

Figure 1. Depicts the anatomy of the upper and lower airways. Adapted from "Bubbles, Babies, and Biology: The Story of Surfactant," by S, Wrobel, 2004, *The Federation of American Societies of Experimental Biology Journal, 18,* p. 1625. Copied by permission from the Federation of American Societies of Experimental Biology. Copyright 2016.

When a newborn begins his or her life as a separate being, he or she must immediately adapt to the extrauterine world by establishing respiratory function and ventilation. This transition involves radical and rapid physiologic change. However, even before these significant events occur at birth, adequate lung development depends on vital intrauterine factors. During the first 20 weeks of gestation, lung development primarily involves differentiation of pulmonary, vascular, and lymphatic structures beginning with the formation of the trachea, bronchi, and lung buds at six weeks gestation. By seven weeks, the diaphragm begins to form and separate the thoracic and abdominal cavities. A definite shape of the lungs is observable by the twelfth week of pregnancy. Before birth the fetus practices breathing movements that aid in the development of lung tissue and strengthen respiratory muscles. These movements may begin around the seventeenth week of pregnancy and continue throughout the pregnancy. These breathing movements facilitate the regulation of lung fluid volume and lung growth. At 24 weeks, the nostrils reopen and the alveoli appear in the lungs and begin producing surfactant. At 38 weeks, the lecithin-sphingomyelin ratio, which is a component of surfactant, approaches 2:1, indicating that surfactant production is sufficient (Davidson et al., 2012).

Alveolar duct formation begins at 20-24 weeks gestation, followed by the formation of primary alveoli at 24-28 weeks. Initially, these alveolar cells begin to differentiate into type I cells necessary for gas exchange and type II cells that provide for the synthesis and storage of surfactant (Martin, 2015). Surfactant is critical for proper alveolar expansion and functioning. It is composed of surface-active phospholipids, lecithin and sphingomyelin, which help keep the alveolar air sacs open during gas

exchange (Davidson et al., 2012). Type II cells begin to increase further between 28-30 weeks gestation, as surfactant is produced within them. Surfactant production peaks at around 38 weeks gestation and continues to be produced until the pregnancy reaches full-term. This is a crucial time when preterm neonates born without sufficient amounts of surfactant exhibit RDS symptoms as a result. Surfactant reduces alveolar surface tension, making it possible for the alveoli to expand and preventing the likelihood of alveolar collapse. Without surfactant, the air spaces are unstable and ineffective at facilitating proper airflow and oxygen uptake. Preterm infants may also have increased respiratory fluid in the alveolar spaces, making effective gas exchange difficult (Martin, 2014a).

The physiology of respiration is broken down into three phases: inspiration, expiration, and respiration. Inspiration is achieved through ventilation, the movement of air into the lungs, while expiration is the opposite, moving air out of the lungs (Eisel, 2014). Inspiration and expiration are accomplished through intrathoracic pressure changes in response to the pressure at the airway opening. Contraction of the diaphragm and intercostal muscles works to decrease intrathoracic pressure, preparing for lung expansion. Naturally, gas flows from an area of higher pressure, in this case the atmospheric pressure outside of the body to an area of low pressure, the intrathoracic space. The process of inspiration takes a higher amount of effort from the body; whereas, expiration is a relatively passive response. The amount of air taken in is determined by the individual's tidal volume (V_T), volume of air exchanged with each breath (Eisel, 2014). A normal V_T for an adult is about 500mL; for a neonate it is much smaller, measured around 5mL/kg (Alapont, Villanueva, & Benavente, 2014). When this amount of air is inhaled, it moves through the bronchioles and terminates at the alveoli, which is

the primary site of gas exchange in the lungs. As previously mentioned, alveoli are very unstable and have the tendency to collapse. To facilitate their expansion, the alveoli secrete surfactant, a lipoprotein that lowers the surface tension, thus reducing the amount of pressure needed to inflate, making them less likely to collapse (Eisel, 2014).

Respiration occurs at the alveolar-capillary membrane (ACM) by a process called diffusion. Diffusion during respiration involves the movement of oxygen and carbon dioxide from an area of higher concentration to an area of lower concentration. Therefore, oxygen moves from the atmosphere air in the alveolar sacs where its concentration is higher, across the ACM and into the pulmonary capillaries where its concentration is lower. At the same time, carbon dioxide diffuses from the pulmonary capillaries across the ACM into the alveoli where it is then expired into the atmosphere during exhalation (Eisel, 2014). The oxygen is then carried by arterial blood back to the heart and pumped throughout the body. The partial pressure of oxygen (PaO2) in arterial blood, and SaO2, the amount of oxygen bound to hemoglobin, measure the oxygenation of the blood. These values are measured by pulse oximetry and arterial blood gases, which give a better clinical picture of the efficiency of gas, transfer in the lungs and overall tissue oxygenation.

The lungs have a capacity of elastic recoil due to the elastin fibers found in the alveolar walls, bronchioles, and chest wall. This elastic recoil gives lungs the tendency to relax after being expanded during inspiration, allowing a passive decrease in volume caused by increased intrathoracic pressure (Eisel, 2014). The ease of lung elasticity while expanding and relaxing is driven by compliance, the distensibility of the lungs. When compliance is decreased, it is harder for the lungs to inflate, making inspiration

challenging. Conditions that decrease the compliance of the lungs include those that increase fluid in the lungs such as pneumonia and atelectasis and conditions that make lung tissue less elastic such as pulmonary fibrosis (Eisel, 2014). Conversely, compliance is increased when alveolar walls are damaged or when elasticity is lost, as in chronic obstructive pulmonary disease (Kaufman, 2014).

Surfactant Deficiency

Another major detriment to respiration is surfactant deficiency. As stated above, surfactant is a lipoprotein produced and secreted by the alveoli to facilitate their expansion during gas exchange. LaPlace's law describes the relationship between inspiratory pressures and surface tension of the alveoli relative to the amount of the alveolar volume. According to LaPlace's law, the pressure (P) needed to keep the alveoli open is proportional to the surface tension (T) and inversely proportional to the radius of the alveolar volume. It is represented by the formula, $P=2T/R$. Therefore, if the surface area is high and the alveolar volume is small as in end-expiration, the pressure required to keep the alveolus open is high (Martin, 2014b). If this high pressure cannot be reached, the alveolus collapses on itself and diffuse atelectasis occurs throughout the lung as more and more alveoli collapse occurs. Atelectasis leads to decreased lung compliance and hypoxemia. Pulmonary surfactant is the key to reducing the surface tension of the alveoli, and even at low volumes it can lead to a decrease in required pressure and maintain alveolar volume and stability (Martin, 2014b). Figure 2 depicts the effect of surfactant and LaPlace's law on the alveolus.

Figure 2. The Effect of Surfactant and LaPlace's Law on the Alveolus

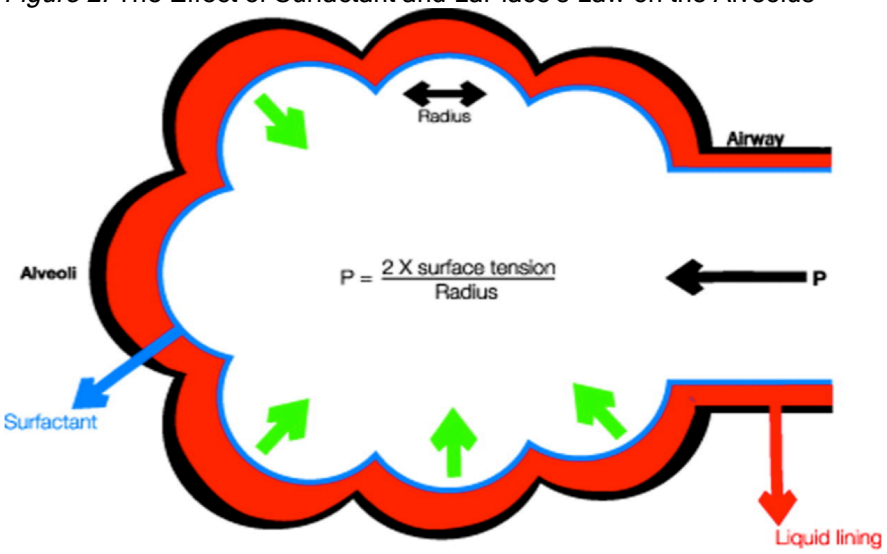

Figure 2. Surfactant forms a thin film (blue) at the air-liquid interface within the alveoli, lowering surface tension and therefore reducing the amount of pressure required to maintain alveolar expansion. Adapted from "Bubbles, Babies, and Biology: The Story of Surfactant," by S, Wrobel, 2004, *The Federation of American Societies of Experimental Biology Journal, 18,* p. 1634. Copied by permission from the Federation of American Societies of Experimental Biology. Copyright 2016.

Pathophysiology of RDS

The characteristic abnormality in the pathophysiology of RDS is surfactant deficiency. The observed deficiency is a direct result of lung immaturity, as surfactant production is not adequate until about 35 weeks gestation (Davidson et al., 2012). In the premature lung, inadequate surfactant production results in increased surface tension, leading to instability in the alveoli at end-expiration, decreased compliance, and resultant low lung volume (Martin, 2014b). These deficiencies in lung function in turn cause hypoxemia due to a mismatch in ventilation and perfusion from diffuse atelectasis and intrapulmonary and extrapulmonary shunts (Brady, 2014). Intrapulmonary shunts occur when the blood flows through the pulmonary capillaries without participating in gas exchange and thus is exhibited in RDS because of the damage at the ACM resulting in the lack of oxygenation. Extrapulmonry shunting would be due to a patent ductus

arteriosus, which is also common in preterm neonates experiencing RDS (Davidson et al., 2012).

Surfactant deficiency not only makes inspiration difficult but expiration as well. If a newborn's lungs lack surfactant, their first inhalation will cause the alveoli to collapse during expiration due to instability of the alveoli. Some oxygen may be absorbed initially by the alveoli, but only a fraction of the oxygen inhaled beyond the first few breaths will be absorbed. This means that continued inspiration would require extra effort to force air into the collapsed alveolar sacs as if every breath were just like the first. The increased respiratory effort would tire out the newborn's diaphragm and tear at the lung tissues, leading to inflammation (Wrobel, 2004).

Lung inflammation and respiratory epithelial injury often accompany RDS in neonates and may result in pulmonary edema and increased airway resistance (Martin, 2014b). Similar to the pathophysiology of acute lung injury and acute respiratory distress syndrome in adults, RDS leads to an inflammatory response, which triggers the release of cytokines and other cell mediators and a mass of macrophages, neutrophils, and platelets to the damaged ACM (Perrin, 2014). The damaged capillary membrane begins to leak, allowing protein-rich fluid to fill the collapsed alveoli, further exacerbating lung injury and disrupting gas exchange. As capillary permeability continues to deteriorate, neutrophils attach to the damaged membrane and may cross into the alveoli. The end stage of this inflammatory response is the formation of hyaline membranes in the alveoli and conduction pathways from the consolidation of proteins (Perrin, 2014).

Clinical Manifestations and Diagnosis

The clinical manifestations of RDS primarily arise from hypoxemia due to abnormal pulmonary function. Preterm birth is most often the cause of deficient surfactant leading to RDS, which is why symptoms present within the first minutes to hours after birth. If untreated, RDS progressively worsens throughout the first forty-eight hours of life (Martin, 2014b). If neonates do not present immediately after delivery in respiratory distress, symptoms are likely to develop within the next few hours. The neonate will exhibit signs of respiratory distress including tachypnea, nasal flaring (reflecting the use of accessory muscles), expiratory grunting resulting from exhalation through a partially closed glottis, showing decreased end-expiratory volume, intercostal, subxiphoid, and subcostal retractions due to decreased compliance and cyanosis due to pulmonary shunting. On a physical, exam breath sounds will be decreased and pulses diminished. Urine output is often low in these infants within the first 24-48 hours of life and pulmonary edema is present (Martin, 2014b).

Diagnosis is often based on the clinical picture in conjunction with characteristic chest x-ray and history of preterm birth. A chest x-ray would reveal low lung volume and diffuse ground glass opacification resulting from atelectasis and pulmonary edema. Other laboratory findings frequently observed in RDS include ABGs revealing hypoxemia with an increasing partial pressure of carbon dioxide (PCO_2) and hyponatremia, which may develop as the disease progresses as a result of fluid retention (Martin, 2014b).

Conventional Treatment Options

Initial management of respiratory distress in neonates, regardless of etiology, often involves supplemental oxygen therapy. Supplemental oxygen may be delivered via facemask, continuous positive airway pressure device (CPAP), or intubation for mechanical ventilation if progressive respiratory distress is observed. Traditionally, noninvasive ventilation is preferred whenever possible, which makes CPAP the most favorable option in most neonatal intensive care units. However, invasive ventilation is often necessary for preterm neonates in respiratory distress (Brown & DiBlasi, 2011). The goal of ventilator therapy is to prevent hypoventilation and hypoxia (Davidson et al., 2012).

In RDS, mechanical lung expansion via CPAP or ventilator helps move the remaining respiratory fluid out of the alveoli and into the interstitial spaces by providing continuous positive pressure or positive end expiratory pressure (PEEP). These methods of mechanical ventilation work to deliver much needed oxygen to the lungs and facilitate gas exchange; however, they do not help the underlying issue of decreased surfactant production. The goal of mechanical ventilation is to maintain oxygen saturation (SpO_2) between 90-95%, which could be measured by continuous pulse oximetry or arterial blood gases (Davidson et al., 2012).

Appropriate fluid and metabolic provision may also be necessary treatment for neonates with RDS; including intravenous fluids and the use of an incubator to maintain a neutral thermal environment to decrease the neonate's energy requirements and oxygen consumption (Martin, 2014a). Prophylactic antibiotics may also be given to reduce the

risk of infection or sepsis if risk factors are present. The duration of antibiotic therapy would be determined by results of a blood culture and chest x-ray.

Another conventional treatment utilized for the prevention of RDS is antenatal steroid therapy. The maturation effect of steroids on the fetus is the rationale behind this treatment option. Antenatal steroids have been shown to reduce the incidence of RDS in the low-birth-weight neonate born between 24 and 34 weeks gestation (Davidson et al., 2012). An amniocentesis can reveal fluid from fetal lungs that can give an indication as to the level of maturation achieved. Antenatal steroid therapy should be based on the analysis of amniocentesis. In a controlled trial of 213 women in spontaneous premature labor, betamethasone or a placebo was given at least twenty-four hours before delivery. Only nine percent of babies born to treated mothers exhibited RDS symptoms, while nearly twenty-six percent of babies born to mothers who received the placebo exhibited symptoms (Wrobel, 2004).

Exogenous Surfactant

Production

The first clinical trials involving exogenous surfactant began in the 1980s. At this point, scientists had made rapid advancements in physiology and biochemistry that provided insight into the mechanisms underlying the development of RDS (Whitsett, 2014). Researchers also achieved a better understanding of the biochemical nature of the lung and the chemical makeup of endogenous surfactant (Wrobel, 2004). Such knowledge was instrumental in the development of both synthetic and natural exogenous surfactant products.

Surfactant has similar components to a cell membrane in that it is primarily made up of proteins and phospholipids. The most abundant constituent of surfactant is the saturated lipid, dipalmitoyl phosphatidylcholine (DPPC), which makes up about 45-70% of endogenous surfactant (Hallman et al., 1994). DPPC acts as a stabilizing agent for a thin film within the alveoli at the interface of liquid and air (Whitsett, 2014). This surface film is responsible for controlling surface tension. As the lung expands, causing tension to rise, DPPC allows the interface to stretch in response and when the lung contracts during expiration, DPPC is responsible for packing in molecules more tightly, thus lowering surface tension and preventing alveolar collapse (Wrobel, 2004). Based on the knowledge of DPPC, an aerosolized form of the lipid was developed and given to several neonates with RDS as a viable treatment option. However, DPPC alone was shown not to be effective in eliminating symptoms entirely (Wrobel, 2004). The problem with DPPC alone is that it does not rapidly absorb in the air-liquid interface in the alveoli, rendering it virtually ineffective (Hallman et al., 1994).

Failure of this approach led to the investigation of the properties of other components of surfactant, mainly unsaturated phosphatidycholine and phosphatidylglycerol, which constitute about 25-45% of endogenous surfactant (Hallman et al., 1994). Phosphatidylglycerol is observed in larger quantities in mature lungs than immature lungs. Phosphatidylglycerol levels do not begin to rise in concentration until about 35 weeks gestation, and therefore, would not be as abundant in premature neonatal lungs. In contrast, immature lungs contain a greater amount of phosphatidylinositol than mature lungs, which has indicated that it is a more immature form of the phospholipid component phosphatidylglycerol (Martin, 2014b).

Other phospholipid components of surfactant include phosphatidylethanolamine and sphingomyelin, a saturated phospholipid with hydrophobic properties. The ratio of lecithin (collection of previously mentioned phospholipids) to sphingomyelin (L/S) is commonly used as an assessment tool of fetal lung maturity and is measured by amniocentesis. An L/S ratio of two to one is ideal for a neonate at birth. Any neonate born before a sufficient L/S ration will have varying degrees of respiratory distress (Davidson et al., 2012).

Four other key components of endogenous surfactant are surfactant proteins A, B, C, and D (SP-A, SP-B, SP-C, SP-D). The discovery of these proteins in endogenous surfactant seemed to answer the question of why previously produced exogenous surfactant containing mostly phospholipids such as DPPC were not effective replacements. SP-B and SP-C were the first proteins to be discovered and proved to be hydrophobic proteins that readily bind to phospholipids (Wrobel, 2004). The reason DPPC alone was not effective as an artificial exogenous surfactant was that it could not move rapidly enough after it was secreted to get to the air-liquid interface in the alveoli to control surface tension. SP-B and SP-C are believed to work together to optimize a more rapid distribution and absorption of phospholipids in exogenous surfactant, allowing for more availability at the air-liquid interface and facilitating lower surface tension and greater alveolar stability (Martin, 2014b).

SP-A and SP-D were more complicated structures to identify, but with advancements in molecular biology, their significance was determined. When compared to other identified biological proteins, SP-A and SP-D identified closely with proteins called collectins, which aid the immune system (Wrobel, 2004). SP-A was the more

major surfactant protein, constituting about 5% of endogenous surfactant; whereas, SP-D was found not only in the epithelial cells of the lungs but throughout the rest of the body, suggesting its immunologic function in the lungs may be more generalized than SP-A.

SP-A is a water-soluble protein with immunologic functions, which serves as an innate host defense protein in the lungs (Martin, 2014b). SP-A facilitates phagocytosis of microbes and their clearance from the airspace. Premature lungs lack SP-A, increasing a preterm neonate's risk for infection; however, corticosteroid therapy has shown to increase its production. SP-A is not present in all forms of exogenous surfactant; though its function is important, it is not critical to survival (Martin, 2014b).

There are many other minor components that make up endogenous surfactant that have been identified, yet their significance has not yet been determined. Many components of the antioxidant defense system, prostaglandins, growth factors, hormones, and chemical messengers all associate with surfactant (Hallman et al., 1994). The main components required of successful exogenous surfactant production include DPPC, SP-B, and SP-C, which are absolutely essential. SP-A and SP-D are still considered major components of endogenous surfactant but not entirely crucial for effective exogenous surfactant solutions.

The two initial goals of exogenous surfactant therapy are efficacy and safety. Other factors include minimal variation, minimal immunogenicity, sufficient resistance to biodegradation, and availability at reasonable cost (Hallman et al., 1994). There are two types of exogenous surfactant that may be utilized: natural and synthetic. Natural surfactant is derived from porcine or bovine lungs through intrapulmonary lavage or by mincing animal lung tissue and purified by lipid extraction, separating hydrophilic

components including SP-A and SP-D (Martin, 2014c). The purified lipid preparation contains SP-B, SP-C, DPPC, and other neutral phospholipids. Human surfactant may also be utilized and isolated in amniotic fluid from full-term fetuses. Synthetic surfactant combines recombinant proteins with synthetic peptides and lipids. Modified natural surfactant may also be supplemented with phospholipid equivalents or other surfactant components (Hallman et al., 1994). Natural surfactants tend to have a faster action of onset and greater improvement in RDS symptoms than do synthetic derivatives. Among the different natural surfactant derivatives there seems to be no clinically significant differences (Martin, 2014c).

The Use and Administration of Exogenous Surfactant

Surfactant therapy is indicated for the treatment of RDS in preterm infants with clinical symptoms. Research now suggests that the prophylactic use of surfactant be integrated into the care of the neonate at risk for RDS (Rojas-Reyes, Morley, & Soll, 2011). Premature neonates less than 30 weeks gestation receive the most benefit from prophylactic surfactant therapy. Exogenous surfactant therapy has significantly reduced mortality and morbidity rates in preterm infants (Martin, 2014c). When surfactant therapy is utilized, the following factors must be addressed:

- Selection of surfactant preparation
- Indications for surfactant therapy
- Timing of administration
- Technical aspects of administration

The types of surfactant therapy available are synthetic and natural preparations. Both types have shown to be effective in treating RDS; however, preparations containing

SP-B and SP-C, which were most often naturally derived surfactant, showed faster improvement in the neonate and relief of respiratory distress. Recent research has shown that natural preparations also contribute to lower inspired oxygen concentration (FiO_2) and ventilator pressures, a lower rate of complications from RDS, and overall decreased mortality rate (Martin, 2014c).

Immediate stabilizing interventions are usually taken prior to the consideration of surfactant therapy. These interventions almost always include the use of either mechanical ventilation via endotracheal tube or the use of continuous positive airway pressure (CPAP) shortly after birth when RDS symptoms are noted. There is data that now suggests nasal CPAP (nCPAP) is just as effective as mechanical ventilation in premature neonates at treating and preventing RDS complications (Martin, 2014c). Nasal CPAP also reduces the risk of bronchopulmonary dysplasia (BPD) by avoiding intubation. The use of nCPAP is consistent with the American Academy of Pediatrics and the European Consensus Guidelines recommendations. Indications for intubation of preterm neonates in severe respiratory distress or apnea include those who do not respond to nCPAP intervention alone and require 40% or higher FiO_2 to maintain an oxygen saturation of 90%. Nasal CPAP is often initiated in the delivery room if respiratory distress is present (Martin, 2014c). Many neonatologists will use increased levels of PEEP and prolonged initial breaths to promote fetal lung expansion and establish functional residual capacity (Herting, 2013).

If nCPAP intervention fails, endotracheal intubation is performed immediately, and surfactant therapy is considered and administered once RDS diagnosis is established and its efficacy is recognized (Martin, 2014c). If the neonate requires greater than 30%

FiO_2 an additional dose of surfactant may be required, according to most clinical research studies (Martin, 2014c). Surfactant is traditionally administered via intratracheal injection through a catheter inserted either through an endotracheal tube or orally introduced to the trachea (Wrobel, 2004). When surfactant therapy is utilized, it is most beneficial when given within the first 30-60 minutes of life. Earlier administration of surfactant therapy has shown to have better clinical outcomes than delayed administration including lower mortality rate and decreased risk of RDS-associated complications including BPD, emphysema, and pneumothorax (Martin, 2014c).

During the administration of surfactant, oxygen saturation should be monitored, as desaturation may occur. Surfactant administration may be complicated by temporary airway obstruction caused by over insertion of the catheter in the airway or inadvertent instillation only to the right stem bronchus (Martin, 2014c). Other possible complications are associated with intubation and prolonged mechanical ventilation, which may cause pulmonary injury due to volutrauma or barotrauma.

Presently, minimally invasive techniques for surfactant administration are being considered and tested, such as less invasive surfactant administration (LISA). LISA advocates for prophylactic administration in the delivery suite for neonates born before 27 weeks gestation. At this age, the premature fetal lung is extremely susceptible to trauma by even short-term therapy on a mechanical ventilator; therefore, nCPAP is utilized immediately after birth and during surfactant administration (Herting, 2013). Close monitoring of neonate's cardiovascular and respiratory efforts is crucial during this procedure. If the procedure is performed beyond the first few minutes of life, peripartal analgesia will be lost and analgesia or sedation should be considered for the neonate if

significant discomfort is noted before attempting to introduce the catheter. Otherwise, the majority of the time, intratracheal catheter administration is done without the use of analgesic medication (Herting, 2013).

Dosing of surfactant administration varies among the available preparations. Suggested dosing strategies range from 50-200mg/kg, depending on the brand and formulation used. Several formulations are in circulation today including synthetic formulations such as Surfaxin®, with an initial dosage of 5.8 mL/kg (DynaMed, 2016). Other forms of surfactant include those derived from the lungs of animals such as calves, pigs, and cows. Infasurf® is a natural surfactant derived from calf lung lavage and has an initial dose of 105 mg/kg or 3mL/kg (DynaMed, 2016). Curosurf® is a formulation of surfactant derived from the lungs of pigs and purified by chromatography (Hallman et al., 1994). The initial dosage for Curosurf® is 200 mg/kg or 2.5 mL/kg (DynaMed, 2016). Another commonly utilized animal formulation of surfactant, Alveofact® has an initial dosage of 50 mg/kg or 1.2 mL/kg (DynaMed, 2016).

Factors such as pharmacokinetics, bioavailability, half-life and concentration in the epithelial lining fluid (ELF) after administration serve as determinants of dosing strategies (Herting, 2013). Type II alveolar cells are responsible for the majority of the catabolism of exogenous surfactant. About 3-7% of the surfactant is cleared by the airways and about 10-30% is taken up by alveolar macrophages. The type II alveolar cells take up the remaining surfactant. In the type II alveolar cells, catabolism of exogenous surfactant occurs in the lamellar bodies and is secreted back in to the ELF for recycling. Recycling of exogenous surfactant incorporates the breakdown of phospholipids in type II cells and reuses them in the synthesis of endogenous surfactant.

Therefore exogenous surfactant increases the amount of endogenous surfactant, contributing further to alveolar stability (Hallman et al., 1994).

Evaluation: The Impact of Exogenous Surfactant

When exogenous surfactant is administered into the airways, it obeys the following pattern. When the surfactant is administered intratracheally, it is rapidly distributed through the patent airways and into the airspaces. During the next one to two hours after administration, the surfactant begins to concentrate in the lung parenchyma; therefore, the amount of surfactant that can be lavaged from the airways decreases. From there, the surfactant continues to congregate in the lung parenchyma and begins to flow into the ELF where absorption occurs and recycling begins. Because surfactant is applied directly to the airways, it does not readily diffuse into the blood stream and therefore blood levels of the drug have little clinical importance. Only a small amount of surfactant components may enter circulation due to high permeability and possible pulmonary edema (Hallman et al., 1994).

In studies of exogenous surfactant administered to rabbits, maturity-dependent differences were recognized, suggesting the same could occur in humans. In adult rabbits, 80% of exogenous surfactant became tissue-associated within less than two hours and about 75% of DCCP was degraded within 24 hours. In contrast, full-term newborn rabbits exhibited about 50% tissue-association and a degradation rate of about 16% within 24 hours. Ventilation may have increased both the degradation rate and tissue-association rate in these animals. These conclusions suggest that a higher dosage would be required for more developed neonates with RDS symptoms (Hallman et al., 1994).

Other factors influencing the bioavailability of exogenous surfactant include: the method of administration, stage and severity of pulmonary disease, and properties of specific type of surfactant such as carrier volume and biophysical properties (Hallman et al., 1994). Generally, about 70-90% of exogenous surfactant administered via bolus-injection through an endotracheal tube reaches the distal airways and alveoli (Dargaville, 2012). A small amount of surfactant may remain in the central airways or may be regurgitated. Positioning the neonate on his or her right and left sides, alternating every few minutes during and after surfactant administration, allows gravity to assist in distribution, reducing the chances of unequal distribution within the lung fields (Hallman et al., 1994). Additionally, repeat dosing of surfactant has been shown through numerous clinical trials to sustain the initial response to the drug in the neonate. Giving multiple doses of surfactant has been shown to decrease the risk of pneumothorax and other pulmonary complications with a clearer clinical outcome expected (Soll & Ozek, 2009).

Further Research

Administration Techniques: Aerosolization

Research involving exogenous surfactant in the treatment of RDS continues today, and focuses on aspects such as formulation, administration, and indications. Administration methods have an impact on the amount of exogenous surfactant utilized by the body and the accuracy of dosing strategies. Current administration techniques include administration with the use of an aqueous carrier, as a dry powder inhalation, and direct endotracheal injection. Administering surfactant with the aid of a saline-containing aqueous carrier increases the volume to be distributed; however, it may have a negative effect on pulmonary edema if it is present. Dry-powder administration of surfactant

counteracts the adverse effects of carrier administration but poses the risk of inadequate distribution or physical obstruction.

Under current review is the administration of surfactant through aerosolization. Aerosolization of surfactant may be the most superior method of administration over endotracheal bolus-instillation or carrier-mediated as far as equal distribution of the drug is considered. However, aerosolization is associated with low bioavailability due to inadequate synchronization of the nebulizer with inspiration of the neonate.

To solve this clinical problem, researchers incorporated the use of CPAP with aerosolized surfactant treatment (Mazela, Merrit, & Finer, 2007). The study reported greater improvement in oxygenation and alveolar ventilation with the use of pharyngeal CPAP with aerosolized surfactant administration versus nCPAP delivery of aerosolized surfactant. The reason for this discrepancy is not entirely clear and requires further clinical trials; however, it may be attributed to the size and clearance of the nasal passageways and dilation of airways. Regardless, aerosolization of surfactant has shown to be more effective because of its biologic properties that enable it to distribute more equally among the lung parenchyma (Mazela et al., 2007).

Pharyngeal Instillation

In theory, the most ideal method of delivery of exogenous surfactant would be to instill it in the airways prior to the neonate's first breath (Hallman et al., 1994). Pharyngeal instillation of exogenous surfactant prior to a neonate's first breath has been undergoing clinical trials since the late 1990s. Pharyngeal instillation is administered during labor before the neonate descends into the vaginal vault. Fetal lung fluid is first suctioned from the airways and replaced with a surfactant-containing solution. By

supplying the surfactant at the air-fluid interspace, it is presumed that the neonate will aspirate the surfactant containing solution, allowing its distribution to the lower airways (Abdel-Latif & Osborn, 2011). This administration technique would allow the replaced fetal lung fluid to be the vehicle of distribution, allowing for a uniform mixing of surfactant in the lungs and subsequent expiration of both fetal lung fluid and excess surfactant upon initial aeration. If administered before the neonate's first breath, distribution would not be disturbed by hyaline membranes that form several hours to two days after birth in a neonate with RDS, nor would there be obstructive pulmonary lesions or edema to inhibit even distribution. This technique also avoids endotracheal intubation and invasive mechanical ventilation, therefore reducing the risk of lung injury. The only disadvantage of this technique is that it is difficult to accomplish and cannot be performed in any compromised labor situation that puts the mother or neonates life at risk (Abdel-Latif & Osborn, 2011).

Dosing Strategies

Another clinical question regarding the administration of surfactant in neonates with RDS is whether multiple or single doses of exogenous surfactant are more beneficial to the neonate. While a single dose of surfactant may relieve respiratory distress symptoms initially, researchers investigated the use of multiple doses in neonates as protocol treatment. A randomized controlled trial performed by Roger Soll and Eren Ozek (2009) involved two groups of neonates, group one consisted of neonates with established respiratory distress and group two consisted of neonates at high risk for respiratory distress. In both research groups, neonates showed greater improvements in oxygenation and ventilator requirements and a decreased risk for pneumothorax with

trends toward improved survival. Giving multiple doses of surfactant to neonates with RDS symptoms appears to be the most effective treatment modality as it leads to improved clinical outcomes (Soll & Ozek, 2009).

Prophylactic Administration

Typically, the treatment for diseases such as RDS begins only after the patient exhibits symptoms. One treatment option for neonates at high risk for RDS includes the antenatal administration of steroids to encourage maturation of the unborn infant's respiratory system. Another method of prophylactic treatment under current review is the administration of exogenous surfactant prophylactically rather than selectively. The theory behind prophylactic administration would be to treat the known cause of RDS in neonates at high risk and thus prevent symptoms from ever occurring, thus decreasing neonatal mortality and morbidity. The prophylactic administration of surfactant was studied in both the term and preterm infant and reviewed by Rojas-Reyes, Morley, and Soll through the Cochrane Neonatal Review Group. Results of the multiple reviewed clinical trials showed significantly decreased risk of pulmonary complications associated with RDS including pneumothorax, interstitial emphysema, bronchopulmonary dysplasia, or death in comparison to selectively treated neonates with established RDS symptoms (Rojas-Reyes, Morley, & Soll, 2012).

Ethical Discussion

Within the last few decades, advancements in medicine and technology have greatly impacted the management of care of the critically ill neonate. Developments in treatment modalities currently being incorporated into the plan of care of severely ill and premature neonates have demonstrated an overall decrease in morbidity and mortality

rates (Strandås & Fredriksen, 2015). The life of the critically ill infant often involves spending months in a neonatal intensive care unit, surrounded by medical staff, ventilators, incubators, and other medical equipment being utilized to save or prolong their life. Unable to speak for themselves, parents are required to make decisions on the infant's behalf, taking into account his or her moral rights and the healthcare team's duty to protect.

Preterm and critically ill infants have long been the subjects of medical research (Strandås & Fredriksen, 2015). Within the context of exogenous surfactant therapy, ethical issues can arise concerning neonatal involvement in clinical trials of the drug involving new administration methods, dosing strategies, and formulations. The question of when to initiate treatment involves a rapid and complex assessment of the risk versus benefit. The ethical principle of nonmaleficence is most often in question among these various research studies and clinical trials as to whether their outcomes are more concerned with the life of the neonate it involves or the efficacy of a newly developed treatment method (Strandås & Fredriksen, 2015).

An important part of the ethical treatment of critically ill neonates lies within the advocating powers of the nurse. The nurse's role is to advocate for his or her patient, not only in the everyday decisions but also often in those involving life-or-death measures. It is the nurse's responsibility and duty to protect their patient from mistreatment, harm, and neglect (Strandås & Fredriksen, 2015). In the neonatal intensive care unit the nurse is responsible for the hands-on care of the neonate. They communicate with the entire healthcare team and work to support the parents through many tough decisions. Nurses should be up to date on the latest medical advancements and treatment methods in order

to effectively advocate for their patient. Ethically appropriate care should be the goal of all treatment modalities and nursing interventions, taking into account the risks, benefit, moral rights and duty to protect.

Conclusion

Today, thanks to much advancement in technology, knowledge, and research in exogenous surfactant therapy, RDS is an uncommon cause of death among neonates in developed nations. Annual death rates from RDS have decreased from 10,000-15,000 babies annually in the United States in the 1950s and 1960s to fewer than 1,000 deaths in neonates annually (Whitsett, 2014). In the midst of incredible scientific discovery, the story of surfactant continues to unfold with new research aiming to answer the questions of why some babies continue to die each year from RDS, including full-term neonates, and what other diseases exogenous surfactant therapy may be useful in treating. Surfactant therapy, in many ways has provided the opportunity of life to babies who otherwise may not have survived. This discovery has demonstrated a positive and perpetual impact on past decades and will for generations to come. Surfactant therapy is truly life saving and should be properly implemented in the neonatal care environment as often and as appropriately as possible.

Appendix

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