Seminars in Fetal & Neonatal Medicine xxx (2017) 1–6

Contents lists available at ScienceDirect

Seminars in Fetal & Neonatal Medicine

journal homepage: www.elsevier.com/locate/siny

Surfactant and continuous positive airway pressure for the prevention of chronic lung disease: History, reality, and new challenges

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Keywords:
Bubble continuous positive airway pressure (CPAP)
Intubation
Less-invasive surfactant
Hyaline membrane disease
Respiratory distress syndrome
Bronchopulmonary dysplasia

A B S T R A C T

The discovery of surfactant was one of the most significant research events to occur in the history of neonatology. Certainly, surfactant saved lives for premature infants who were otherwise considered non-viable. However, the prevention of chronic lung disease did not progress and it became clear that a significant portion of the help surfactant provides to the premature lung is counteracted by mechanical ventilation. A dilemma exists over the priorities in premature management to intubate and administer surfactant or not to intubate and support these infants non-invasively with the use of continuous positive airway pressure. A new hydrophilic surfactant preparation has been developed with the hope to enable the introduction of surfactant therapy without the need for tracheal intubation. Clinical trials on this product are currently in progress. This article provides the history and prospect of respiratory distress management in premature infants and evaluates the current evidence for non-invasive practices.

1. Respiratory distress syndrome

The pathogenesis of respiratory distress syndrome (RDS) in premature lungs has been thoughtfully hypothesized in the eighteenth century. Joseph Raulin, a French obstetrician, noted that when immature lung "vesicles" are too weak, they do not accept atmospheric air and subsequently blood vessels collapse and the infant would die [1]. In 1835, Eduard Jörg, a German obstetrician, described a new disease different from birth asphyxia that occurs in premature babies born with immature "fetal lungs." He advocated minimal handling and warming for their management. Jörg was the first to report a relationship between use of oxygen and the development of gross inflammation in the airways [1]. However, these findings did not change the then popular forensic practice to differentiate postnatal infant death from in-utero fetal demise. The "floating test" wrongly assumed that excised parts of the lung would not float on water surface only because of fetal death and would not consider the option of a neonatal death with immature collapsed lungs.

The microscopic description of hyaline membrane disease (HMD) was developed in the twentieth century. Components of the hyaline membrane were initially thought to be aspirated from amniotic fluid; however, because these components were later found to contain fibrin, it was theorized that HMD was caused by coagulation abnormalities in the systemic or pulmonary circulation. For several years, research focused on how to dissolve this fibrin-rich membrane, for example, with the use of fibrinolytic agents [2], or how to prevent fibrin deposition using plasminogen. This membrane was perceived to be the consequence of another disorder rather than the original cause of RDS. This wrong perception was empowered by the findings of a few randomized trials demonstrating reduced mortality when plasminogen was administered intravenously to newborns with RDS [3]. Of note, during this time the administration of antenatal glucocorticoids was known to improve respiratory outcomes of premature infants [4].

Knowledge on the mechanics of breathing in neonatal lungs has grown so much in the 1940s. More important than tissue elasticity, the increased surface tension in premature alveoli was shown to be the determining factor for their recoil, collapse, and resistance to aeration. This was demonstrated in 1947 by Gruenwald, a pathologist in New York, who measured the pressure required to inflate lungs of deceased newborns with and without the introduction of saline [5]. When saline was introduced into the lungs, they required

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http://dx.doi.org/10.1016/j.siny.2017.08.001
1744-165X/

much less pressure to inflate. Interestingly, these same findings were unknowingly reported in Europe by the Swedish physiologist, Kurt von Neergaard, in 1929 [1].

2. Surfactant deficiency and discovery

After completing her pediatric residency at Johns Hopkins in 1957, Mary Ellen Avery started a fellowship training to study newborns with Clemente Smith at Brigham and Women's Hospital, then called the Lying-In Hospital, and to do research in Jere Mead's laboratory at Harvard. This physiology laboratory was particularly interested in measuring the dynamic force of elastic recoil in the presence and absence of fluid in the lung; using a thermodynamic modeling for the pressure–volume data, they could calculate the internal surface area of the lungs [6]. However, the calculated surface area of the lung was significantly less than the measurements established with morphometry. This discrepancy could only be reconciled if calculations were based on a very low surface tension inside the lung [7]. In 1959, Avery and Mead were the first to introduce the concept that HMD occurs due to lack of surfactant and not because of secretion or aspiration of a fibrin-rich materials [8]. Once deficiency of surfactant was recognized as the true problem in premature lungs, research focused on extracting, manufacturing and experimenting its administration for the cure of premature infants with HMD. After multiple attempts, it was recognized that introducing only the phospholipid component of surfactant via nebulization would not work [9]; whereas administration of the whole surfactant to premature animals was successful [10]. Only in 1980 was the first study on endotracheal administration of surfactant in premature infants published by Fujiwara and his colleagues [11]. Subsequently, hundreds of premature infants were enrolled in multiple randomized trials to examine safety, efficacy, dosing and other clinical aspects of this life-saving medication [12]. Table 1 summarizes historical landmarks for RDS and surfactant discovery.

The discovery of surfactant is one of the most significant research events to occur in the history of neonatology. It signifies a phenomenal breakthrough event that excelled at all stages including sound animal physiology research, biomedical drug development, collaboration of government, pharmaceuticals and scientists, and clinical application via well-designed randomized controlled trials.

3. Surfactant administration and dosing

Since 1980, multiple clinical trials have been conducted on thousands of infants to examine different aspects of surfactant therapy. Once surfactant had been administered to an infant, immediate improvement in oxygenation was noticed that continued for up to 36 h. The improved oxygenation was better sustained when multiple doses were used. The timing and strategy of surfactant administration have been studied. For example, the prophylactic administration of surfactant before resuscitation in the delivery room was more efficacious than the rescue treatment where surfactant was administered to infants after presenting the signs of respiratory distress a few hours later in life. The amount of surfactant treatment and the optimal number of doses to be administered have also been studied. Additionally, various types of surfactant were compared; earlier studies showed natural surfactant to be more efficacious than synthetic surfactant (which did not contain any protein) in reducing mortality of infants at <30 weeks of gestation [13]. Newly introduced synthetic surfactant contains a peptide that mimics surfactant protein B; this new version showed benefits that are at least comparable to those produced by natural surfactant [14]. Different types and sources of animal-derived natural surfactant have been compared [15].

4. Surfactant effects on neonatal outcomes

It is beyond the scope of this communication to describe the details of clinical trials on surfactant or to list all efficacy outcomes of these trials. However, it is important to summarize the impact of surfactant use on specific outcomes of premature infants that will clarify what has already been established and what is yet to be achieved. It is also important to note that in early surfactant trials (1980–2005), premature infants in the control group who did not receive surfactant therapy were supported with mechanical ventilation (Fig. 1). Table 2 summarizes findings of the key clinical trials on surfactant therapy during this phase.

4.1. Mortality

The relationship between lack of surfactant and mortality has been established for decades. A famous incident of mortality due to RDS was the death of Patrick Bouvier Kennedy, son of President John F. Kennedy, who was born prematurely at 34 weeks and died with RDS in 1963. The use of surfactant significantly decreased mortality of premature infants. When compared to control groups, prophylactic use of surfactant reduced mortality to a greater extent than when used as a rescue therapy [13,16]. Surfactant was recognized as one of a very few inventions that significantly reduced mortality without a known side-effect.

4.2. Air leak

Pneumothorax and other types of pulmonary air leaks

Table 1
Selected historical landmarks for the discovery of respiratory distress syndrome (RDS).[a]

Year(s)	Landmark
1768	Premature infants were noted to die because immature lung “vesicles” did not accept atmospheric air (Raulin).
1925–49	Hyaline membrane was thought to result from aspirated amniotic sac contents.
1950	Clinical signs of RDS were described.
1951	Hyaline membrane was thought to be a transudate from plasma protein due to atelectasis and tissue damage.
1953–55	Description of the radiographic reticulogranular pattern of RDS as a separate entity from aspiration pneumonia.
1953–57	Hyaline membrane was found to be primarily made of fibrin.
1955–1956	Scoring system developed for clinical quantification of the severity of RDS.
1955–1956	Surfactant was discovered in pulmonary edema foam and in lung extracts.
1959	Pulmonary surfactant deficiency was discovered in premature infants who died with RDS (Avery).
1959	The name “RDS” was introduced as a synonym to hyaline membrane disease.
1973	Antenatal glucocorticoids were used for the prevention of RDS.
1980	First surfactant replacement therapy was administered to premature infants (Fujiwara).

[a] Modified from Clement and Avery [12].

Please cite this article in press as: Aly H, et al., Surfactant and continuous positive airway pressure for the prevention of chronic lung disease: History, reality, and new challenges, Seminars in Fetal & Neonatal Medicine (2017), http://dx.doi.org/10.1016/j.siny.2017.08.001