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(REVIEW ARTICLE)

The evolution of surfactant replacement therapy: From pathophysiology to noninvasive clinical strategies

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Abstract

Background: Respiratory Distress Syndrome (RDS) continues to be a major factor in neonatal health issues and fatalities, particularly in preterm babies. While Surfactant Replacement Therapy (SRT) has been the accepted treatment since the 1990s, advancements in respiratory support, like the transition to noninvasive ventilation, demand a fresh look at the types of surfactants and their delivery methods.

Objective: This review investigates the pathophysiology of RDS, the biochemical structure of pulmonary surfactants, and how effective various treatment strategies are, including a comparison between natural and synthetic solutions along with invasive and noninvasive techniques.

Methods: This research combines information from randomized clinical trials and meta-analyses that examine surfactant storage pools, the functions of surfactant proteins (SP-A, B, C, and D), and the timing of interventions (preventive versus rescue).

Results: Currently, natural surfactants that come from animals are favored because they contain important hydrophobic proteins (SP-B and C), although newer synthetic options such as Lucinactant are promising in minimizing batch variability and the risk of immune reactions. There is strong clinical evidence that supports administering "early rescue therapy" within 1 to 2 hours of birth instead of waiting for treatment. In addition, techniques like Less Invasive Surfactant Administration (LISA) and INSURE have greatly lowered the need for mechanical ventilation and have reduced the occurrence of bronchopulmonary dysplasia (BPD).

Conclusion: SRT serves as a fundamental component of neonatal intensive care, greatly decreasing mortality rates and the occurrence of pulmonary air leaks. Current practices in neonatology are shifting from routine intubation to a more selective approach that includes rescue therapy along with noninvasive support. Upcoming developments are focused on enhancing synthetic peptide analogues and nebulized delivery methods to further reduce lung damage.

Keywords: Respiratory Distress Syndrome (RDs); Surfactant Replacement Therapy (SRT); Preterm Infants; DPPC (Dipalmitoylphosphatidylcholine); Surfactant Proteins (Sp-B, Sp-C); Less Invasive Surfactant Administration (Lisa)

1. Introduction

After the first successful report of surfactant replacement therapy (SRT) in infants with respiratory distress syndrome (RDS), several randomised clinical trials have indicated that SRT decreases mortality and morbidity associated with

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RDS [1]. As a result, surfactant has become a standard treatment for this condition. Due to the high occurrence of respiratory distress syndrome (RDS) in premature infants and its considerable role in neonatal illness and death, improvements in neonatal intensive care have raised survival rates, particularly for babies born at 24 to 26 weeks' gestation, However, respiratory failure secondary to surfactant deficiency remains a critical challenge in this population [2,3]. Administering exogenous surfactant delivers a precise treatment that stabilises respiration until enough functional type II cells can generate and secrete endogenous surfactant. The key reason for using surfactant treatment in ARDS is the surfactant dysfunction present in the injured lungs [4]. Consequently, developing synthetic surfactants that are more resistant to inactivation and can be produced in a cost-effective manner for large-scale production to meet the needs of adult patients could be beneficial [5].

The growing use of noninvasive ventilation as the main form of respiratory support has changed how clinicians administer surfactant. This review looks into the pathophysiology of RDS, surfactant composition, the clinical evidence backing surfactant therapy, and new strategies for administering it. The main reason for neonatal RDS is either a lack of surfactant or its improper function caused by underdeveloped lungs [6,7]. By lowering the surface tension at the air-liquid interface, surfactant prevents alveolar collapse during expiration and aids in improving lung compliance [8].

In its absence, increased surface tension can cause atelectasis, a decrease in functional residual capacity, difficulty in gas exchange, and greater breathing effort. Consequently, newborns typically exhibit tachypnea, retractions, grunting, and hypoxemia shortly after delivery, with the greatest severity normally appearing within the first 12 to 48 hours, and potential complications may include pneumothorax, the necessity for mechanical ventilation, bronchopulmonary dysplasia (BPD), peri-intraventricular haemorrhage, and mortality [9,10].

A substance called a surfactant decreases the surface tension found between two liquids [11-15]. In 1950, the word surfactant was coined to denote molecules featuring hydrophobic and hydrophilic sections within a single structure. Surfactants fall into four main types: cationic, anionic, zwitterionic, and non-ionic [16-20]. When these substances are at a particular concentration called the critical micelle concentration (CMC), they form micelles.

2. The Composition and Function of Pulmonary Surfactant

The fundamental function of pulmonary surfactants is to diminish surface tension, preventing alveoli from collapsing at the end of expiration. This mixture includes roughly 90% lipids and 10% proteins, with lipids accounting for 80%–90% phospholipids, 5% neutral lipids, and cholesterol. The main components of phospholipids are 80% phosphatidyl-choline, 5% to 10% phosphatidyl-glycerol (PG), and additional phospholipids, while DPPC and PG are the primary surface-active phospholipids that effectively decrease surface tension [21,22].

3. The Role of Surfactant Proteins (sps)

Surfactant proteins (SPs) are made up of two hydrophobic proteins known as SP-B and SP-C, together with two hydrophilic proteins, SP-A and SP-D. The roles of SP-B and SP-C are vital in the adsorption and spreading of DPPC to maintain alveolar stability since phospholipids with SP-B and SP-C are secreted directly into the airspace in lamellar bodies. Phospholipid layers called surface films are formed at the air-liquid interface, where SP-B and SP-C also help stabilize this surface film during respiration. Furthermore, DPPC can adsorb to the air-liquid interface of alveoli through hydrophilic head groups with an affinity to water and with the hydrophobic tail directed toward the air, thus effectively reducing surface tension [23]. The surfactant storage pool for term infants is at 100 mg/kg, but in preterm infants, it is just 4–5 mg/kg upon birth. Consequently, it is critical to provide exogenous surfactant therapy to preterm infants until their own surfactant levels become high enough to stabilize the alveoli and lessen surface tension [24].

4. Clinical Impact of Surfactant Replacement Therapy

In the early 1990s, surfactant replacement therapy (SRT) had been established as a safe and effective approach for treating surfactant deficiency due to immaturity [25]. Consistent evidence from randomized controlled trials and meta-analyses indicates that SRT notably decreases mortality, reduces pulmonary air leak syndromes, and lessens the overall outcome of death or BPD by day 28 [26,27]. Furthermore, Long-term follow-up research indicates that there is no rise in harmful neurodevelopmental effects in infants who received surfactant treatment [28,29]. As a result, these results collectively endorse SRT as a fundamental therapy in neonatal intensive care.

4.1. What type of surfactant is preferable – Natural or synthetic?

No matter what form is chosen, it is useful in treating RDS because it is a complex structure largely consisting of dipalmitoylphosphatidylcholine (DPPC) paired with surfactant proteins SP-A, B, C, and D [30]. Within this arrangement, SP-B and SP-C are two hydrophobic proteins that are important for the adsorption and distribution of DPPC on the alveolar surface. Hence, since the late 1990s, many systematic reviews have summarised a broad range of literature on clinical trials that compare various types of surfactant to establish clinical superiority.

4.2. Natural Surfactants

The concept of 'natural surfactant' is not straightforward since, if taken literally, it is defined as a surfactant that comes directly from natural sources, which may be plant or animal-based [31]. The resultant product should be derived through a separation process like extraction, precipitation, or distillation, without engaging in any organic synthesis, not even as a final treatment. There are actually few surfactants used today that comply with these strict requirements, although lecithin from either soybean or egg yolk is perhaps the best example of a genuine natural surfactant. The main reason true natural surfactants are rare is not that they are unavailable; rather, amphiphiles are plentiful within both the plant and animal kingdoms, often called polar lipids. These surface-active agents in biological systems are used much like surfactants in technical environments to tackle solubility challenges, work as emulsifiers, serve as dispersants, and modify surfaces [32]. Furthermore, Surfactants from animals are obtained from the lungs of cows or pigs and include phospholipids along with surfactant proteins SP-B and SP-C [33]. These specific formulations closely mimic endogenous human surfactant and have proven to be clinically effective; however, they have limitations that include high costs, potential variability between batches, the theoretical risk of pathogen transmission, and rare occurrences of hypersensitivity reactions [34,35].

4.3. Synthetic Surfactants

Synthetic surfactants were specifically created to lessen variability and eliminate the risks tied to animal-based products [36]. These innovative synthetic formulations feature peptide analogues of SP-B and SP-C paired with phospholipids, with the goal of replicating the functional attributes of natural surfactants. As a result, clinical trials have shown that these synthetic alternatives are both feasible and safe, while further comparative studies are still being conducted to assess their long-term effectiveness compared to treatments derived from animals.

5. What is the need for newer synthetic surfactants?

While animal-derived surfactants are preferred for the prevention and treatment of RDS, they come with serious issues, such as lower SP-B levels than human surfactants, variations in SP-B concentration across lots, and the inclusion of various potentially immunogenic foreign proteins in these products. Consequently, the initiatives aimed at solving these challenges have produced significant progress in the formulation of new surfactants, such as those that incorporate recombinant SP-C (rSP-C), which is still being advanced but has not yet begun clinical trials in infants [37]. Similarly, surfactants containing SP-A offer another avenue worth exploring, since studies involving SP-A knockout mice show positive results [38]. Lucinactant, a newly FDA-approved synthetic surfactant, includes an SP-B analogue called Sinapultide that efficiently mimics SP-B function. This formulation shows improved resistance to oxidation and protein inhibition compared to surfactants from animals; additionally, aerosolizing it does not notably change its physical characteristics [39].

6. Timing strategies: prophylactic versus rescue therapy

The timing for giving surfactant includes two key approaches: prophylactic surfactant administration, which is the early delivery right after birth for high-risk infants before they show serious respiratory problems, and rescue therapy, given after a clinical diagnosis of confirmed RDS, usually within the first 12 hours of life [40]. The extensive use of early continuous positive airway pressure (CPAP) suggests that routine prophylactic intubation might increase the risk of lung injury. Therefore, systematic reviews have shown that the use of early CPAP paired with selective rescue surfactant can diminish the occurrence of chronic lung disease or fatal outcomes compared to regular prophylactic intubation [41].

7. Early versus delayed rescue therapy

Promptly administered rescue therapy, known as surfactant treatment within the first 1–2 hours of life, has shown better clinical results than treatment given later. Meta-analyses regularly highlight considerable decreases in mortality, air leak, chronic lung disease, and the overall outcome of death or BPD when early intervention is utilized [42]. As a result, the current international recommendations advise the prompt administration of selective rescue surfactant

when clinical signs of RDS are detected [43]. Additionally, using surfactant before moving preterm infants between hospitals has been associated with decreased oxygen requirements during transport and a reduced length of ventilation support compared to controls [44].

8. Methods of Surfactant Administration

The INSURE approach entails briefly intubating to deliver surfactant, and this is immediately succeeded by a fast extubation to CPAP [45]. This technique is effective in providing the required treatment; however, it's essential to keep in mind that even short instances of positive-pressure ventilation employed during the process may result in lung injury. The LISA technique for administering surfactant employs a fine intratracheal catheter, allowing the infant to breathe spontaneously under CPAP [46]. Clinical research shows that this method leads to less reliance on mechanical ventilation and a decreased occurrence of BPD compared to conventional intubation techniques [47,48]. Consequently, LISA is becoming more popular as a favored method in numerous neonatal centers around the globe. Administering nebulized surfactant with vibrating membrane technology shows potential as a noninvasive alternative to standard methods. Early studies imply this technique is viable, but inconsistent outcomes and small sample sizes require more comprehensive clinical trials to establish its effectiveness [49,50].

9. Repeat Surfactant Dosing and Ongoing Clinical Management

Some babies experiencing persistent RDS might need surfactant treatments more than once because studies indicate that administering multiple doses when necessary, leads to better outcomes [51]. Consequently, according to international guidelines, repeat dosing is advised in situations where there is a sustained requirement for oxygen or ongoing ventilatory assistance to ensure sufficient lung stabilization, other considerations regarding use of surfactant preparations [9]. There are many natural and synthetic surfactants available, each with varying concentrations of SP and phospholipids, as well as different dosing recommendations. While the effectiveness reported may differ based on the preparations, these variations could stem from differences in study sites rather than real variations in efficacy [52]. Reports indicate that the timing of surfactant administration, whether prophylactic or rescue, and whether it's given early (within 2 hours of birth) or delayed (after 2 hours of birth), is more crucial than the actual composition of the surfactant preparations [53]. Moreover, the way surfactants are given is more important than what they are made of, as a noninvasive ventilator might improve lung health in premature infants [54]. Less invasive surfactant administration was attempted by the continuous positive airway pressure or intubation at birth trial and the SUPPORT (Surfactant, Positive Pressure, and Pulse Oximetry Randomised Trial) study [55,56].

The use of less invasive surfactant administration combined with intubation and quick extubation to nasal respiratory support (InSurE) has lowered the need for ventilator support, resulting in the development of new surfactant administration approaches such as Minimally-Invasive Surfactant Therapy and Non-Invasive Surfactant Therapy. Future Directions and Clinical Implications, Surfactant therapy is still one of the most significant treatments in neonatology as it reliably lowers mortality rates, pulmonary air leaks, and the overall incidence of death or bronchopulmonary dysplasia (BPD) [57], Consequently, Future studies need to aim at enhancing delivery techniques, fine-tuning timing strategies, and combining surfactant treatment with advancing noninvasive respiratory support technologies to boost neonatal care.

Abbreviations

- **RDS:** Respiratory Distress Syndrome;
- **ARDS:** Acute Respiratory Distress Syndrome;
- **BPD:** Bronchopulmonary Dysplasia;
- **CPAP:** Continuous Positive Airway Pressure;
- **NIV:** Non-Invasive Ventilation;

10. Conclusion

Surfactant Replacement Therapy has positively impacted the survival rate of preterm infants with RDS. The shift from standard preventive intubation to early selective rescue therapy, inspired by advancements in noninvasive ventilation, indicates a crucial evolution in clinical methods. Although animal-based surfactants are currently favored in clinical settings for their excellent adsorption capabilities, the emergence of synthetic surfactants such as Lucinactant tackles issues related to expense, scalability, and safety in biological contexts, It is now acknowledged that the administration method is as crucial as the surfactant formulation itself. Techniques like LISA and INSURE signify an important

advancement in shielding the sensitive lungs of neonates from the damage caused by mechanical ventilation. Ultimately, the best opportunity for improving long-term neurodevelopment and lung outcomes in this vulnerable group lies in merging high-efficacy synthetic surfactants with truly noninvasive delivery methods, such as nebulization.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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