

Fellows Column: Surfactant: To Use or not to Use

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Case Report

An infant was born via normal spontaneous vaginal delivery at 28 ²/₇ weeks gestation to a 26-year-old G₂P₁ woman with no chronic medical conditions. The mother was Group B Streptococcus (GBS) negative, rubella immune, HBsAg negative, and had consistent prenatal care. A short cervix and premature labor had complicated the pregnancy. Antenatal steroid therapy was completed, and the membranes were ruptured just before delivery. Delayed umbilical cord clamping was performed for 30–60 seconds. The newborn weighed 1290 grams and required continuous positive airway pressure (CPAP) and hand ventilation at delivery. Apgar scores were 9 and 9 at 1 and 5 minutes, respectively. The infant was admitted to the neonatal intensive care unit (NICU) for respiratory failure, prematurity, and observation for presumed sepsis. Upon admission, the infant was placed on High Flow Nasal Cannula (HFNC) with Noninvasive Mechanical Ventilation (NIMV) at a peak inspiratory pressure (PIP) of 18, positive end-expiratory pressure (PEEP) of +5, and a fraction of inspired O₂ (FiO₂) of 0.30. Antimicrobial therapy for presumed sepsis was started. CBG levels were measured at a pH of 7.326, pCO₂ of 54.8, pO₂ of 39.2, HCO₃ of 28.6, and a base excess of 2.6. A chest X-ray at two days of age showed diffuse reticular opacities bilaterally. At this time, the neonatologist on duty chose to withhold surfactant administration.

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On day 2, FiO₂ levels on NIMV were lowered to 0.28 and then to 0.21 on day three without signs of respiratory distress. A repeat chest X-ray on day 5 demonstrated persistent, granular ground glass attenuation bilaterally, raising concerns for possible respiratory distress syndrome (RDS). Surfactant administration was again withheld at this time. Nares and blood cultures investigating neonatal sepsis were negative; however, the WBC was markedly elevated at 69.2 beginning on day two and remained elevated throughout the week. Furthermore, several episodes of apnea and bradycardia were noted in the first week but had all self-resolved. The infant remained stable for two weeks and was switched from NIMV to bubble CPAP at a PEEP of +5 and an FiO₂ of 0.21 without complications. A 9-day course of both ampicillin and gentamicin was completed, with WBCs returning to normal

levels after two weeks. Throughout recovery, the infant received a continuous IV infusion of caffeine citrate and tolerated feeds well. With each subsequent weaning trial, the infant appeared stable without any signs of cyanosis or increased work of breathing (i.e., retractions, grunting, nasal flaring).

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Introduction:

Our research suggests that surfactant administration may not always be imperative, challenging the conventional assumption and thus highlighting the need for individualized neonatal care strategies based on clinical assessment and comprehensive evaluation of respiratory status. A cross-sectional retrospective study concluded that 37.5% of surfactant prescriptions were irrational (1). Surfactant administration, though crucial in certain situations, should be prescribed more judiciously and not universally. We aim to challenge the conventional approach to surfactant administration in the NICU.

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Surfactant Physiology:

Pulmonary surfactant is a complex mixture of 70–80% phospho-

lipids, which are primarily composed of dipalmitoylphosphatidylcholine (DPPC), 10% proteins, including SP-A, -B, -C, and -D, and 10% neutral lipids, mainly cholesterol (2). Surfactant production initiates at approximately 26 weeks of gestation and reaches mature levels around 35 weeks. This essential substance is synthesized in the endoplasmic reticulum (ER) of type II pneumocytes and is subsequently released from the lamellar bodies of these cells (3). Surfactant is a crucial substance in the lungs, especially for neonates, as it plays a key role in respiratory physiology. Its primary functions include:

1. **Reducing surface tension** at the air-liquid interface within the alveoli (tiny air sacs in the lungs) (4).
2. **Facilitating breathing**, as the presence of surfactant allows the lungs to expand more easily during inspiration, take in enough oxygen, and expel enough carbon dioxide. These are essential processes for maintaining proper oxygen levels in the blood (4).
3. **Preventing atelectasis**, which is the collapse of lung tissue, and surfactant helps prevent this by keeping the alveoli open (4).
4. **Immunological properties** strengthen the defense mechanisms of the respiratory system, protect the lungs from infections, and contribute to the overall health of the respiratory tract (4).

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Surfactant undergoes a process of synthesis, assembly, transport, secretion into the alveolus, subsequent degradation, and recycling. In newborns, particularly preterm infants, surfactant metabolism is slower than in adults (2). Issues in pulmonary surfactant metabolism can lead to respiratory distress, causing significant morbidity and mortality. This is often a result of accelerated breakdown due to factors like oxidation, proteolytic degradation, inhibition, or inherited defects in surfactant metabolism (2). Understanding the physiology of surfactant use in neonates is crucial for managing the respiratory health of preterm infants and those at risk of respiratory distress. Current management strategies for these defects include the administration of prenatal corticosteroids, surfactant replacement, whole lung lavage, and, in some instances, lung transplantation. Gene therapy has emerged as a potential avenue for addressing inherited defects in surfactant metabolism, offering promising prospects for treatment (2).

Current Criteria for Surfactant Administration:

Current guidelines for surfactant administration suggest that infants born at less than 24 weeks gestational age should undergo

immediate intubation upon birth, with prophylactic surfactant administration recommended within the first 15 to 30 minutes of life (5). For infants born at or beyond 24 weeks gestational age who are immediately intubated after birth, it is suggested to administer surfactant as an early treatment within the first two hours of life (5). Exceptions to these guidelines are made if the infant is breathing room air with minimal ventilatory support upon admission to the NICU (5). An immediate transition to nasal ventilation or continuous positive airway pressure is recommended (5).

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These guidelines are particularly relevant when faced with specific clinical indicators, including:

- a) Maintaining an FiO_2 above 0.5 to achieve an oxygen saturation (SpO_2) exceeding 88% or a partial pressure of arterial oxygen (PaO_2) surpassing 45 mmHg
- b) Maintaining a partial pressure of arterial carbon dioxide (PaCO_2) within the range of 55 mmHg to 60 mmHg with a pH level below 7.25
- c) Experiencing apnea requiring bag and mask ventilation
- d) Displaying evidence of significant work of breathing, such as retractions, grunting, and chest wall distortion in infants with increased oxygen needs (5)

Alternatives Methods to Surfactant Delivery:

In current medical practice, the most widely accepted method for administering surfactant is through endotracheal instillation (3). This method involves delivering the surfactant in a liquid form through an endotracheal tube, using a single bolus dose as quickly as a neonate can tolerate (3). While some studies suggest

administering the entire surfactant dose at once, others propose dividing the bolus into smaller aliquots (3). This decision is often left to the discretion of the healthcare providers (3).

Another approach to surfactant delivery, the INSURE (INTubation-SURfactant administration-Extubation) technique, involves an in-out intubation procedure to administer surfactant (3). This process involves intubation, surfactant administration, and extubation (3).

Current research is focused on newer methods to reduce the invasiveness of traditional approaches, with one such technique being minimally invasive surfactant therapy (MIST) (3). MIST involves connecting a neonate to non-invasive respiratory support, allowing surfactant administration to occur through spontaneous breathing (3). An alternative approach is the less invasive surfactant administrative (LISA) technique, which utilizes a flexible, thin catheter placed in the trachea during spontaneous breathing for surfactant delivery (3). Typically, this method requires support with CPAP, eliminating the need for intubation and thereby reducing the risk of potential lung injury associated with intubation (3).

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Adverse Effects of Surfactant Delivery:

Since surfactants are derived from animal sources, there is a risk of immune activation (3). The administration of surfactant in neonates has also been associated with hypotension, bradycardia, alterations in cerebral flow, and hypoxemia (3). Other observed effects of surfactant delivery include intraventricular hemorrhage, patent ductus arteriosus, retinopathy, necrotizing enterocolitis, and complications arising from the endotracheal tube blockage (3). Furthermore, the concurrent use of oxygen presents the potential for lung tissue damage due to oxygen pressure, and excessive oxygenation followed by cessation may result in conditions like bronchopulmonary dysplasia and retrolental fibroplasia in infants (3). There have also been reports of oxygen desaturation occurring upon the drug's administration (3).

The conventional methods of surfactant delivery, which involve endotracheal administration, carry inherent risks associated with

tubal administration of any drug (3). Maintaining hygiene is crucial, especially in neonates with underdeveloped immune systems, as the absence of preventive measures has been associated with infections and sepsis (3). Intubation, a prerequisite for surfactant delivery unless the neonate has already been intubated, poses risks such as injury, air leaks, airway obstruction, and mechanical damage, often requiring frequent suctioning (3).

A retrospective cohort study examining infants born between 24 and 31 weeks found that 30% experienced CPAP failure within the initial 72 hours of life following MIST administration (6). Additionally, the research revealed that MIST failure was independently linked to a heightened risk of severe intraventricular hemorrhage (6). Another study examined surfactant administration in 39 infants and found that 19 infants presented with some complication afterward, 11 minor and 8 major (7). Of the major complications, severe airway obstruction and persistent pulmonary hypertension were most common and associated with extremely low birth weight (7).

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Discussion:

The presented case prompts reconsideration of the conventional surfactant administration protocol. This patient's favorable progression without surfactant delivery suggests that rapid surfactant administration in preterm infants may not always be crucial. Unnecessarily using surfactant is invasive and can pose a risk of harm to the newborn (3).

Historically, the death of John F. Kennedy's son catalyzed the research surrounding RDS and the use of surfactants (8). More recently, the focus in this field has shifted towards refining surfactant administration and reducing its invasiveness, leading to the development of the LISA and INSURE techniques (3). While these methods have addressed the risks associated with intubation and preservation of spontaneous breathing, the paradigm shift towards less invasiveness in surfactant administration highlights the ongoing evolution in neonatal care, emphasizing a commitment to enhancing the delicate balance between therapeutic efficacy and minimizing potential complications.

Surfactant administration does not come without risk, and the potential adverse effects of surfactant delivery should be considered when treating patients. Potential complications such as hypotension, bradycardia, and immune activation should be weighed against the benefits of treatment, and the necessity of treatment must be carefully examined. Surfactant facilitates

breathing, reduces surface tension, prevents atelectasis, and improves immune protection. The presented case challenges the immediate necessity of surfactant in particular situations. Although our neonate, in this case, was born preterm with diffuse reticular opacities in the lungs, surfactant was not administered, and the patient's respiratory function improved.

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Our findings are corroborated by the retrospective cohort study that determined that not all infants receiving MIST had positive outcomes, emphasizing the need for more cautious treatment guidelines (3). Additionally, another study concluded that CPAP with or without surfactant administration had equal efficacy and illustrates the unnecessary invasiveness, risks, and costs associated with surfactant use, especially in low socioeconomic countries (9). Moreover, other research has suggested stricter guidelines for surfactant administration to reduce nonessential surfactant treatment. Multiple sources have recommended including FiO_2 as a criterion for prescribing surfactant, suggesting that it should only be prescribed if the FiO_2 requirement exceeds 0.30, 0.40, or 0.50 (10, 11, 12). Further research needs to be done to determine concrete treatment guidelines that consider FiO_2 requirements as well as EGA and steroid therapy. NICUs should aim to provide personalized neonatal care strategies based on detailed clinical assessment and respiratory status.

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