Exogenous surfactant: intubated present, nebulized future?

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Background: **Exogenous surfactant is currently administered via intra-tracheal instillation, a method which can increase the possibility of clinical instability in the peri-surfactant administration period. Since its introduction, there has been an increase in understanding of the pathology of respiratory distress syndrome and surfactant biology. This includes development of a potential nebulized surfactant which has the potential to increase the number, safety and timely administration of the medication in preterm infants.**

Data sources: **Based on recent original publications in the field of surfactant biology, we reviewed our experience with surfactant administration and discussed the available evidence on nebulized surfactant and outlined potential barriers toward widespread introduction of this therapy.**

Results: **Surfactant has revolutionized modern neonatal management and nebulized surfactant is attractive and a vector for administration. However, issues regarding cost-effectiveness, development of nebulizer devices capable of administration, deposition of medication in the airway and dosing strategies remain unresolved.**

Conclusions: **Nebulized surfactant has the potential to be a therapeutic breakthrough by eliminating the potent volu-and-baro-traumatic effects of mechanical ventilation in the peri-surfactant period. Nebulization would likely lead to increased administration immediately after birth and more emphasis on non-invasive ventilator strategies. These features will aid clinical implementation of nebulized surfactant as a standard of treatment after introduction.**

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Review article

Introduction

Surfactant replacement therapy (SRT) has been a mainstay of treatment for preterm respiratory distress syndrome since its introduction in 1990.[1] SRT has decreased the incidence of death, pneumothorax, and intra-ventricular hemorrhage, and improved survival of preterm infants.[2] Currently intra-tracheal administration is the only approved means of delivery, requiring endotracheal intubation and its attendant comorbidities. The purpose of this article is to review basic mechanism of surfactant biology, provide insight into current modes of administration and present the rationale and data for nebulized surfactant—a novel delivery system for the treatment of respiratory distress syndrome. As an increasing number of non-invasive ventilation strategies are developed, the utility of administering SRT without intubation has the potential to reduce intubation complications and reduce the volu-and-baro-traumatic effects associated with mechanical ventilation.

Basic properties of pulmonary surfactant

Pulmonary surfactant is synthesized by Type II pneumocytes, held in lamellar bodies and released in the airspace as tubular myelin.[3,4] Surfactant comprises 80% phospholipids—the most common being dipalmotyl phosphatidylcholine, 8% lipids such as cholesterol and 12% surfactant proteins, named A-D. Surfactant serves to reduce surface tension, a role assisted by its dynamic properties at the air-water interface in response to altered stretch and tidal volume breathing.[5,6] This function is predominantly mediated by surfactant proteins B and C, which promote formation of a phospholipid monolayer at the alveolar surface. In general, surfactant precursors (glycerol, fatty acids, choline and glucose) are obtained from the

circulation and are transported to the lamellar bodies. Surfactant proteins are synthesized in the endoplasmic reticulum of type II pneumocytes, glycosylated in the Golgi appartus and also transported to lamellar bodies for storage. Lamellar bodies release their contents into tubular myelin at the air-water interface (Fig.). Surfactant proteins A and D are large, hydrophilic molecules involved in host-defense. These proteins bind micro-organisms, regulate chemotaxis and phagocyte function, and promote cytokine production. Ninety percent of surfactant is conserved and the entire circulating surfactant pool is replenished every 9-10 days.[7] Surfactant components are recycled via receptor-mediated endocytosis, reincorporated in lamellar bodies, and then re-secreted during recycling.

Indications and efficacy of exogenous pulmonary surfactant

Indications, timing and mechanism of SRT for neonates remain areas of active research. Data are available on SRT for other respiratory conditions including meconium aspiration syndrome, congenital surfactant protein B deficiency, congenital diaphragmatic hernia and pediatric and adult acute respiratory distress syndrome (ARDS).[8-11] Meconium aspiration syndrome alters mechanism of respiration, causing decreased lung compliance and ventilation/perfusion matching, increased airway resistance, functional residual capacity and respiratory work.[12] Meconium inactivates surfactant, resulting in inflammation and atelectasis. Exogenous surfactant is thought to restore this inactivated pool, and has resulted in short-term improvement in oxygenation index and a subsequently decreased need for extra corporeal membrane oxygenation.[13] However, a 2000 systematic Cochrane review demonstrated a reduced need for extra-corporeal membrane oxygenation without statistical decreases in pneumothorax, chronic lung disease or mortality.[14] Stevens and Sinkin[2] found that these studies were performed before the widespread use of inhaled nitric oxide, which has further decreased their impact and underscores the need for a randomized controlled trial aimed to assess the utility of exogenous surfactant in meconium aspiration syndrome. Similarly, a randomized trial of surfactant in pediatric ARDS showed no difference in primary outcome of ventilator-free days. However, short-term benefit in secondary outcomes of oxygenation index and mortality were seen.[10] Currently surfactant is not recommended routinely for congenital surfactant protein B deficiency, congenital diagphragmatic hernia or adult ARDS, though no randomized control trials have been performed.

Administration

Currently surfactant administered within 2 hours of life to infants less than or equal to 28 weeks gestational age reduces the incidence of pulmonary interstitial emphysema (PIE), chronic lung disease, pneumothorax and mortality.[15] For infants at high risk of respiratory

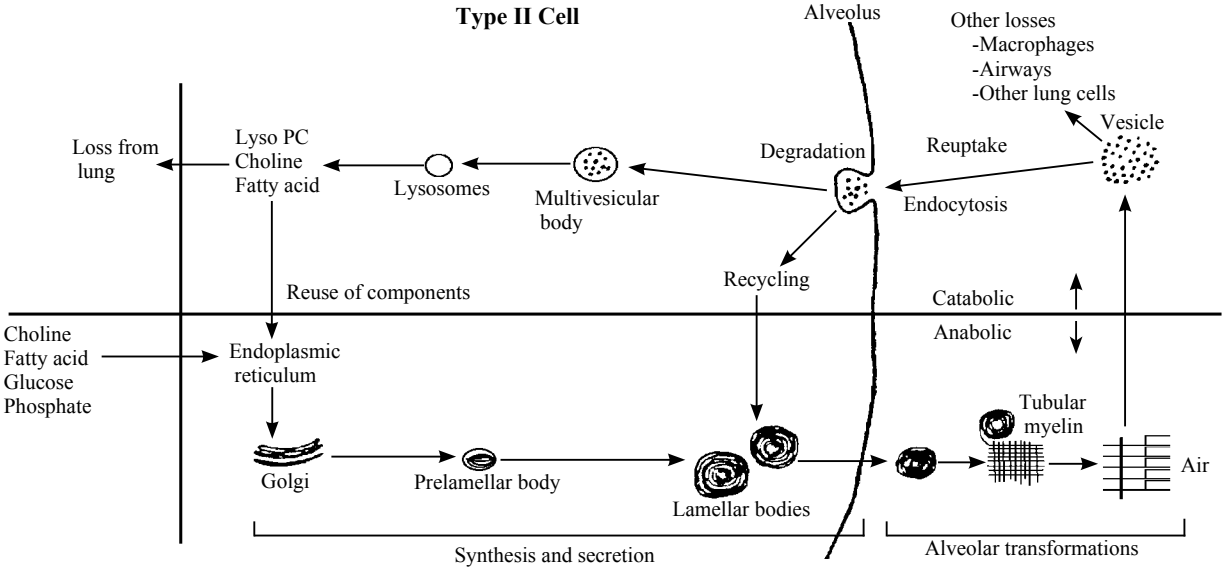

Fig. Schematic of surfactant synthesis and secretion: pulmonary surfactant's choline and fatty acid backbone is synthesized in the endoplasmic reticulum of type II pneumocytes. Surfactant is stored in pre-lamellar bodies and secreted at the air-interface as tubular myelin. Approximately 10% of surfactant is utilized per day, with components taken up by receptor-mediated endocytosis into the cell, stored in multi-vesicular bodies and destined for recycling. (Image courtesy of Dr. Pradeep Mally).

distress syndrome who receive surfactant within 30 minutes of life, reductions in PIE, death, grade III and IV intraventricular hemorrhage and the combined outcome of broncho-pulmonary dysplasia and death were seen in comparison with infants who receive surfactant later in life. These meta-analyses included patients who received both synthetic and naturally-derived surfactant. Natural versus synthetic surfactant was compared in a large scale meta-analysis by Soll et al.[16] This review concluded that both types of surfactant are effective in treatment of respiratory distress syndrome (RDS) when given for established RDS or as prophylaxis. However, animal-derived surfactants resulted in fewer deaths. For these surfactant preparations, the number needed to treat to prevent one death was 37. Sinha et al[17] noted that this review was driven to statistical significance for natural surfactants based on a study which was prematurely terminated and not intended as a head-to-head comparison of natural versus synthetic surfactant, but rather as a pharmaco-economic study.[18] Noteworthy is the comparison also took place using older generation synthetic surfactant preparations.

Endotracheal instillation is the only current means of surfactant delivery. Administration maximizes clinical outcomes when delivered with substantial positive end expiratory pressure (PEEP), improving uniformity of distribution.[19-21] But timely administration of surfactant is difficult to achieve. Even among infants less than 29 weeks who require intubation in the delivery room, administration of surfactant within 30 minutes with PEEP is poor.[22] The increasing popularity of the T-piece resuscitator, which provides more uniform PEEP compared to Bag-Mask ventilation and is addressed in the Neonatal Resuscitation Program as an alternative to bag ventilation, may increase the rapidity of prophylactic administration.[23,24] Since PEEP is more uniformly distributed, concerns regarding inconsistent, low or excessive PEEP in the peri-surfactant period may be eliminated, allowing safer delivery-room administration without the need for a ventilator to provide consistent PEEP. Consistency of pressure is vital, as changes in both positive inspiratory pressure and PEEP can contribute to increased volu-and-baro-trauma, heralding the inflammatory changes within the lung which are associated with chronic lung disease.[20]

Intubation is associated with several comorbidities. Right main stem bronchus intubation, pneumothorax, esophageal perforation, accidental extubation, and obstruction of the tube are well known complications of this procedure. Apneic events, transient hypoxia, oxygen saturations, bradycardia and alterations in blood pressure and intracranial pressure are also linked to intubation events.[25] For infants born outside level III units, intubation is likely to be performed by a provider infrequently exposed to the procedure, with increasing risk. Pediatric trainees showed poor competency in intubation skills.[26-29] The high efficacy of surfactant therapy in reducing complications of prematurity, coupled with the high risk of intubation complication and decreased skills amongst trainees and providers at community centers makes a nebulized delivery system an appealing option to improve the speed of surfactant administration.

Considerations of nebulized surfactant

Two different types of nebulizers are generally available to physicians. Ultrasonic nebulizers provide a high nebulization rate of a liquid drug preparation, but are not considered effective for high viscosity liquids. As a consequence of nebulization, heat is produced, which may destabilize drug formulations.[30] Jet nebulizers generally use a compressed gas source to force air through a nozzle, creating mist for inhalation. Effective delivery of aerosolized medications is dependent upon the mass median aerodynamic diameter (MMAD), defined as the droplet diameter above and below which 50% of the drug's mass is contained.[30] MMAD is critical in determining the delivery of aerosol via inertial, impaction and sedimentary forces—the 3 processes which govern movement of aerosols within distinct generations of airway branching.[31,32] These factors are considered particularly critical for nebulized surfactant delivery as increased inertial forces in the upper airways can increase deposition, clogging airways and subsequently increasing resistance. This will impact the volu-and-baro-traumatic effects of positive pressure administration, further impeding transmission of the medication distally along the airway. Several patient-related factors have also been identified in nebulized medication delivery. Inspiratory flow rate, tidal volume, respiratory rate, upper airway and breath holding time are important considerations for premature newborns requiring surfactant.[33] Premature neonates have increased airway resistance, small tidal volumes (per kilogram) and altered anterior upper airway anatomy compared to adults. Ideal particle MMAD for infants has not been adequately established.[30,34] Furthermore, patient size may be a consideration for dosing, an important consideration given that of 4 clinical trials reported, 3 used fixed doses for delivery regardless of patient size.[35] The technical aspects of nebulized surfactant was best described elsewhere.[36]

Briefly, Jorch et al[36] used two doses of 150 mg/kg of undiluted natural bovine surfactant attached to a jet nebulizer via T-piece connector. This apparatus was connected to a naso-pharyngeal tube advanced to just

beyond the soft palate. The flow of the nebulizer was set at 8 liters/minute and the doses administered over 5-20 minutes. Berggren et al[37] also used a jet nebulizer connected directly to the CPAP adaptor in his trial with a flow of 7 liters/minute. Finer et al[38] utilized new nebulizer technology (Aeroneb Pro) requiring only 1 liter/minute of flow as well as a synthetic surfactant preparation, which may better survive the rigors of nebulization.

Clinical data

Analysis of the 4 published clinical studies evaluating the efficacy of nebulized surfactant is difficult as the studies varied in preparation, delivery device and designed outcome. Jorch et al[36] determined continuous positive airway pressure (CPAP) and nebulized alveofact compared with CPAP alone resulted in improved alveolar-arterial gradient and arterial carbon dioxide levels in infants between 28-35 weeks gestational age. A comparison of nebulized Curosurf and CPAP versus CPAP alone in infants of 23-36 weeks gestational age found no difference in clinical outcomes, but demonstrated that nebulized surfactant was safe and well tolerated.[37] Similarly, Finer et al[38] showed the safety of nebulized lucinactant in 17 patients between 28-32 weeks of gestational age. As has been noted previously, 3 of these studies used a fixed amount of drug and dose was not weight based.[38,39] Full comparison of all studies is available from Mazela et al.[35] Table briefly summarizes the four studies and is adapted from this reference.

Drawing from past studies of nebulized medications in cystic fibrosis patients and the history of intratracheal instillation, it is reasonable to suggest weight-dependent dosing and studies of respiratory performance are both clinically relevant indices in evaluating nebulized surfactant dosage. Studies comparing nebulized vs. intratracheal surfactant and powered to examine not only respiratory outcomes but morbidities of prematurity such as mortality, chronic lung disease, retinopathy of prematurity, intraventircular hemorrhage and necrotizing enterocolitis are required to further evaluate nebulized efficacy. Since Marshall et al[25] reported transient desaturation episodes with administration, a long-term study of neurodevelopmental outcome should also be considered. To date, the only surfactant preparation with sufficient data to report retention of biological activity after nebulization is lucinactant—a synthetic preparation consisting of DPPC, palmitoyleleoyl, phosphatidyl glycerol, palmitic acid and KL4, a novel synthetic peptide similar to surfactant protein B.[35]

Exogenous administration of surfactant has led to increased survival and decreased morbidity of premature infants. Its use for pediatric and adult ARDS has not been well established beyond short-term improvements in secondary outcomes and therefore is not routinely recommended. Delivery of surfactant requires intubation, and is best administered within 30 minutes with CPAP to maximize outcomes in infants of less than 28 weeks and within 2 hours for infants of 28-32 weeks, again with CPAP support. With the increasing popularity of the T-piece resuscitator to administer CPAP in the delivery room and the time-dependent nature of surfactant administration, nebulized surfactant is appealing. Such a system may prevent intubation for some patients, thus decreasing the risk of complications with the procedure. However, questions regarding this promising technology, including survival and activity of the medication after the nebulization process, MMAD size, weight-based dosing and indications for use need to be clarified. A randomized controlled trial compared to intra-tracheal instillation of surfactant, powered to look at not only short-term morbidities but long-term neurodevelopmental outcome should be considered before widespread adoption of this therapy over current standards of care.

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Table. Comparison of four clinical experiences with nebulized surfactant for respiratory distress syndrome in preterm infants*

Study	Gestational age (week)	*n*	Surfactant dose	Primary outcome
Jorch et al[36]	28-35	20	Natural bovine surfactant 150 mg/kg × 2	Improvement in A-a gradient and $PaCO_2$
Berggren et al[37]	27-34	34	Minced porcine surfactant 480 mg	Safely tolerated, no improvement
Finer et al[38]	28-32	17	Synthetic surfactant 108 mg total phospholipid dose	Procedure safe and tolerated well
Arroe et al[39]	23-36	22	Synthetic surfactant 108 mg phospholipid with increasing dose	No improvement in a-A ratio

*: Table adapted from Mazela et al.[35]

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