2007

Secondary Surfactant Dysfunction and Deficiency

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SECONDARY SURFACTANT DYSFUNCTION AND DEFICIENCY

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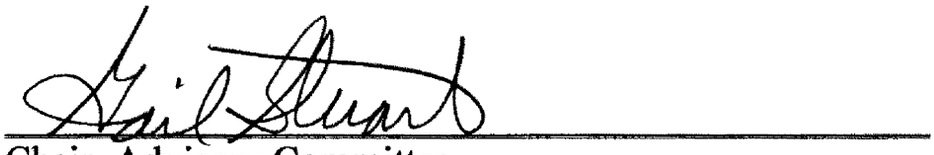
A dissertation submitted to the faculty of the Medical University of South Carolina in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Colleges of Graduate Studies.

College of Nursing

March 9, 2007

Approved by:



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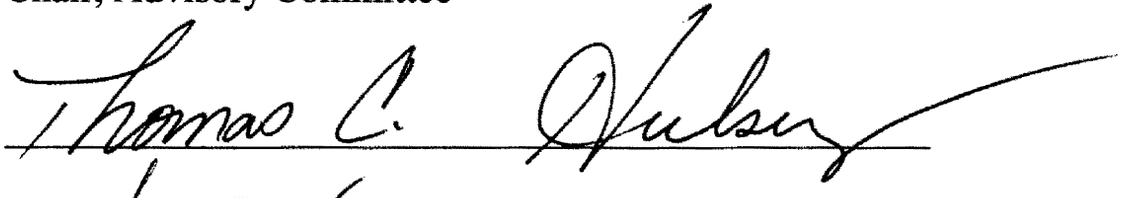

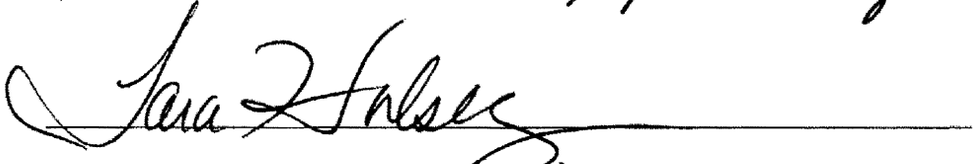

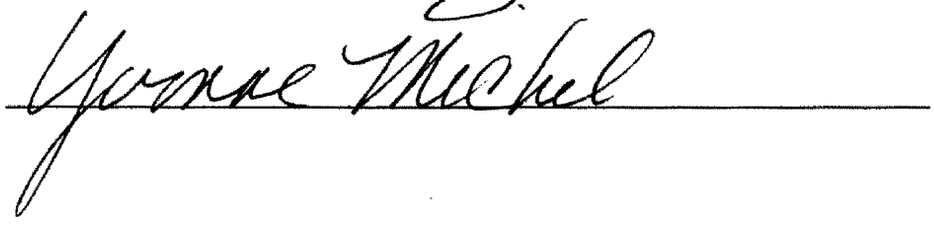

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ABSTRACT

Based on literature in Adult Respiratory Distress Syndrome in humans and evidence of surfactant activation in vitro and vivo, and our clinical observations of secondary respiratory decompensation in premature infants recovering from RDS, a study was designed to look at the possibility of benefit from secondary surfactant administration in premature infants with secondary decompensation after recovery from respiratory distress syndrome (RDS). A prospective pilot study was performed to study the effects of secondary surfactant administration on oxygenation, ventilation and pulmonary function of neonates who had respiratory decompensation after recovery from RDS. A secondary data analysis was performed looking at pulmonary function related to ventilatory efficiency index (VEI), modified ventilatory index (MVI) and respiratory severity score (RSS).

Entry criteria included infants admitted with RDS who were 7 days to 3 months of age, with birth weights $\geq$ 500 grams. Infants qualified if they demonstrated recovery from RDS with a secondary respiratory decompensation defined prospectively as an acute pulmonary decompensation after 6 days of age, which was non-cardiac in origin and accompanied by diffuse parenchymal lung disease on chest x-ray, in conjunction with sustained increase in fraction of inspired oxygen (FiO_2; $\geq$ 20%) and mean airway pressure (MAP; $\geq$2 cm) above base-line for at least 4 hours prior to surfactant administration. Infants meeting all entry criteria received surfactant within four hours of

the qualifying decompensation and again 12 hours later. Oxygenation, ventilation and pulmonary function were compared before and after administration at 12 and 24 hours.

Twenty neonates qualified for secondary surfactant administration. The PCO_2, pH, MAP, FiO_2, MVI, and RSS all improved significantly at 12 and 24 hours after surfactant administration. Infants who received Curosurf had improvement in pH and PCO_2 within 2 hours of surfactant administration. The rates of adverse events were low.

These findings suggest that secondary surfactant administration may be effective in reducing short term oxygen and ventilatory requirements and improving pulmonary function in neonates who have a respiratory decompensation after recovery from initial RDS. Secondary surfactant replacement may improve outcomes in this subset of patients and further randomized controlled trials are needed to confirm these preliminary findings.

ACKNOWLEGEMENTS

I give my sincere thanks to the many people who have helped me to accomplish those tasks required of a doctoral student. I would like to express a special thanks to Dr. Gail Stuart, Dr. Thomas Hulsey, Dr. Tara Hulsey and Dr. Yvonne Michel, my dissertation committee. They have been dedicated to my success and have allowed me the autonomy to think out of the box and accomplish my dreams and aspirations within the confines of doctoral education. I thank Dr. Stuart for taking the time to mentor a student while taking on the role of Dean and Dr. Hulsey and Hulsey for always being there. I thank Dr. Michel for making statistics exciting, teaching me SPSS and following through with my dissertation even after retirement.

I thank Dr. Marilynn King for making me thing about concept analysis and understand the depth of questions such as "How do you know you know?" I also thank the rest of the MUSC doctoral faculty who taught me the wisdom of their experiences and encouraged me to keep going even when the going seemed too rough. I want to give a special thanks to Linda Bellig who encouraged me to go to school and obtain a masters degree years ago and then pushed me to pursue the thesis option. It was during that time that I realized how much I loved research and statistics and this drove me to continue my education.

I would like to thank the Neonatal Nurse Practitioner team at MUSC who were part of this study. This team helped me survive the education process and offered me friendship and support. They are a group of individuals I can depend on as a source of strength. I would like to thank Dr. Doe Jenkins who took the time to mentor me and the NNP team

at MUSC to take on a research in an area that was new and unknown. She never let us quit. Also thanks to the other doctoral students who have shared my road. We made it and I look forward to working with you through-out our careers.

Of special important to me is my family, whose love, confidence and encouragement helped me through these past few years. To my wonderful parents who taught me that nothing is impossible if you really want it. To my grandmother who spent her last 5 years asking me every time she saw me if I was a doctor and who died before I could finish this dissertation "I love you". Your spirit has pushed me to graduate and I know that you have watched over me throughout this process. To my three daughters, Bresney, Che'lynne and Eden who have grown up watching their mother study at night and on weekends. I hope I have instilled in you the drive to always learn and achieve your dreams in life. I am so proud of all you are becoming. Most of all I want to thank my husband Gary who has taken care of the house and our lives for the last 6 years, you are my strength and I love you. I love all of you and thank God for each of you daily. It is the faith and belief in God that has truly shaped and guided my life and I am forever in his mercy.

"The mind of man guides his way, but the Lord directs his steps"

Proverbs 16:9

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INTRODUCTION

Infants born prematurely, especially those less than 30 weeks gestation are at high risk for lung disease at birth. The clinical pattern after the first week of life usually includes episodes of respiratory decompensation necessitating increased inspired oxygen or ventilatory support [1]. The requirement for respiratory support often continues for weeks [2, 3]. In 30% of low birth weight infants lung disease will progress to Bronchopulmonary Dysplasia (BPD), defined as a continuing requirement for supplemental oxygen and /or positive pressure ventilatory support at 36 weeks postmenstrual age [4, 5]. The progressive respiratory failure in these infants is probably multifactorial secondary to oxygen toxicity, volutrauma associated with mechanical ventilation, infection, patent ductus arteriosus (PDA), and inflammation, and results in arrest of alveolar development and interstitial fibrosis [4]. In some infants this respiratory decompensation can lead to respiratory failure and subsequent death.

Trials are currently investigating the administration of surfactant to adults and children with Acute Respiratory Distress Syndrome (ARDS), but neonatal health care providers are just now recognizing this disease process in premature and term neonates. Secondary episodes of respiratory decompensation in neonates are frequently severe, requiring intensive ventilation and systemic therapy, increasing time on the ventilator (at a time when many infants are ready to extubate), and may contribute significantly to development of BPD. Surfactant replacement distributes a more uniform tidal volume among the alveoli and might reduce the damage caused by mechanical ventilation while helping to decrease atelectasis, improve lung compliance and decrease intrapulmonary

shunting. The administration of exogenous surfactant in neonates with pulmonary hemorrhage, pneumonia, sepsis, aspiration or pulmonary edema, who have clinical evidence of ARDS, may expedite recovery, diminish morbidity and lower the cost of care for these infants.

BACKGROUND AND SIGNIFICANCE

More than 500,000 infants are born premature each year and most will have respiratory distress syndrome at birth [6]. The administration of exogenous surfactant has proven to be efficacious in the treatment and prevention of neonatal RDS, a syndrome characterized by primary surfactant deficiency. It is, in fact, standard of care for the respiratory treatment of RDS, and is being investigated in the therapy of other lung diseases [7]. A recent meta-analysis performed by the Cochrane Neonatal Review Group stated:

"Clinical trials have proven that surfactant therapy is effective in improving the immediate need for respiratory support and the clinical outcome of premature newborns [8]. Trials have studied a wide variety of surfactant preparations used either prophylactically or in the treatment of established respiratory distress syndrome. Using either treatment strategy, significant reductions in the incidence of pneumothorax as well as significant improvement in survival has been noted." [8]"Early surfactant administration has been shown to significantly decrease the risk of pneumothorax, pulmonary interstitial emphysema (PIE), chronic lung disease and neonatal mortality." [9]

Surfactant administration has significantly improved the outcome of infants with RDS but despite this improvement approximately 30% of infants with birth weights < 1,000 grams will develop BPD, often from secondary respiratory failure, leading to long term pulmonary and/or neurodeveolpmental disability or death in severe cases [4, 5]. Animal and human studies have demonstrated that surfactant deficiency and inactivation

accompany other diseases, which can cause secondary respiratory decompensation in neonates who are recovering from RDS. [10] Secondary surfactant dysfunction (SSD) may be the result of many factors:

- Inactivation of the surfactant by plasma proteins that pass into the alveolus
- Inhibition or damage to the protein or phospholipid component of the surfactant by inflammatory mediators
- Incorporation of surfactant into hyaline membranes
- Alterations of the synthesis, storage, or release of surfactant as a result of damage to type II pneumocytes
- Loss of surfactant caused by high volume mechanical ventilation
- Interference with reuptake/recycling of surfactant phospholipids and proteins

Secondary surfactant dysfunction (SSD) causes respiratory decompensation often leading to respiratory failure by decreasing compliance and functional residual capacity of the lung, resulting in atelectasis and pulmonary edema. Preliminary data demonstrate that the administration of exogenous surfactant may be safe and efficacious in ameliorating the respiratory decompensation seen in infants who develop pulmonary hemorrhages, pneumonia, sepsis, or pulmonary edema. These disease processes in neonates are similar to ARDS. Surfactant deficiency and inactivation have already been correlated with ARDS, suggesting injury to type II alveolar cells [11]. According to the 1994 consensus definition, ARDS is the acute onset of respiratory failure in an adult or child with bilateral pulmonary infiltrates on chest radiograph, hypoxemia (quantified by PaO2/ FiO2 of $\leq$ 200), and absence of left atrial hypertension. [12] Risk factors include sepsis, pneumonia and aspiration of gastric contents. Trials are currently investigating the

administration of surfactant to adults and children with ARDS, but neonatologists have been slow to recognize this disease process in premature and term neonates. Neonatal care-givers are trained in the use of surfactant in primary surfactant deficiency (RDS) but largely do not consider the possibility of SSD with acute respiratory decompensation that occurs after the initial course of surfactant. The administration of exogenous surfactant in neonates with pulmonary hemorrhages, pneumonia, sepsis, aspiration or atelectasis who have clinical evidence of ARDS may expedite recovery, diminish morbidity and lower the cost of care for these infants. Studies are needed to analyze the safety and efficacy of surfactant in conditions, which may involve SSD in neonates who have recovered from RDS.

SURFACTANT DYSFUNCTION AND DEFICIENCY

Pulmonary surfactant maintains normal lung function by lowering the surface tension at the air-liquid interface. Respiratory distress syndrome is directly related to surfactant deficiency unlike ARDS which is a more complex lung disease with surfactant deficiency and dysfunction along with secondary lung damage. ARDS patients have alveolar instability, atelectasis, and reduced pulmonary compliance leading to ventilation-perfusion mismatch, intrapulmonary shunting, hypoxia and increased work of breathing with the need for mechanical ventilation [13]. Lung lavage studies and studies on autopsy have been able to show surfactant alterations in patients with ARDS type symptoms.

Hallman and colleagues looked at bronchoalveolar lavage (BAL) samples in patients with ARDS and found these patients had abnormal surface properties [14]. Pison and colleagues also looked a BAL samples in patients with ARDS and found a decrease in surface tension [15]. Gregory and co-workers looked at BAL samples and found that

patients at highest risk for developing ARDS had lower surface tensions [16]. These studies and others indicate that surfactant dysfunction and alterations in surface tension correlate with respiratory severity in ARDS [13]q

Studies have also shown alterations in surfactant composition in patients with ARDS. There are decreased quantities of both the lipid components of surfactant and the surfactant proteins [16-18]. The biochemical and biophysical status of surfactant was analyzed in 32 infants with RDS who received surfactant, 12 infants with RDS who did not receive surfactant and 8 infants without RDS [19]. Surfactant therapy resulted in the rapid rise of surfactant protein B and albumin with stable surfactant function. A rise in surfactant protein A and albumin occurred more slowly over 48 hours. Higher levels were associated with decreases in respiratory severity with a rapid fall in the ventilatory index. These researchers stated that surfactant replacement in infants with RDS increases the surfactant concentrations and reduces lung injury. They found that infants with subsequent relapse had surfactant dysfunction and not deficiency [19]. Several studies have shown decreased levels of surfactant protein A which is important in host defense, facilitating phagocytosis by macrophages [16, 17, 20-22]. Beresford and Shaw, 2003, looked at BAL samples in premature infants who died in the first two weeks of life compared to those who survived and found lower levels of surfactant protein B [23]. Merrill and colleagues also found decreased levels of surfactant protein B in tracheal aspirates from premature infants < 30 weeks gestation, who required mechanical ventilation beyond the first week of life and experienced a secondary respiratory deterioration measured by a worsening RSS [24]. Merrill and colleagues analyzed 247 tracheal aspirate samples in a prospective study of 68 infants between 23-30 weeks

gestation who remained intubated at 7-84 days of life [24]. They found that 75% of premature infants < 30 weeks gestation who still required mechanical ventilation beyond the first week of life had dysfunctional surfactant associated with both infection and respiratory deterioration measured by their respiratory severity score [24]. They also showed an association with a decrease in both surfactant protein B and surfactant protein C. These findings supported the timing and mechanism for secondary surfactant dysfunction or post surfactant slump [24]. Surfactant proteins play a crucial role in normal surfactant function and metabolism and further investigations related to these proteins and composition of surfactant preparations may be critical to recovery in many patients with ARDS.

The phospholipids and surfactant proteins must be actively recycled by the type II pneumocytes. Damage to the type II pneumocytes with lung injury impairs the secretory and recycling pathways and leads to surfactant deficiency. Exposure to 85-100% oxygen has been shown to cause type II cell hypoplasia and death [25]. Decreased amounts of surfactant will allow for pulmonary edema with leads to a viscous circle of inactivation and edema formation [26]. With the decreased amount of surfactant the alveoli collapse and mechanical ventilation leads to over expansion and damage to normal lung in attempt to recruit the injured lung, again leading to further injury and edema. Further research regarding dosing amount and administration timing are needed to learn how to break this cycle.

Multiple substances have been shown to interfere with surfactant function. Surfactant function is affected by surfactant inactivation with the earliest study showing inactivation of surfactant by plasma or serum [27]. Pulmonary edema was first correlated with

surfactant inactivation by Avery and Said relating it to hyaline membrane formation [28]. Albumin, globulins and fibrinogen mix with surfactant interfering with its absorptive properties which increases surface tension [29, 30]. These substances compete for the surface area. Surfactant has since been shown to be inactivated by oxygen free radicals, proteins, amino acids, lipids and toxins [16, 17, 31-36]. Takasuke and colleagues looked at clinical and biochemical factors associated with surfactant dysfunction and found that pulmonary hemorrhage inhibited surfactant activity [37]. Ongoing inactivation in some patients may indicate the need for multiple doses during the acute stages of disease. Optimal timing for treatment in premature infants who have recovered from RDS but have a respiratory decompensation later in their recovery is unknown.

RESPIRATORY SEVERITY

There have been many indices used to assess respiratory severity in adults, children and neonates. In neonates respiratory severity has been associated with risk of death from respiratory failure [38, 39]. Commonly used parameters of respiratory failure have included the alveolar-arterial oxygen tension differences, the ratio of arterial to alveolar oxygen tension, and the oxygen index. All of these parameters require arterial blood gas analysis to obtain the PaO_2. Arterial blood gas analysis is not always possible and other parameters are being used or modified to assess respiratory severity in neonates including the RSS, VEI and the MVI.

The RSS [Fraction of inspired oxygen (FiO_2) x MAP] is a modification of the oxygen index ($OI = [(FiO_2) \times (MAP) \times 100]/ PaO_2$) without the need for PaO_2 values, allowing for a simple measure of the severity of lung disease in intubated patient with the same oxygen saturation goals. Mean airway pressure (MAP) has a direct relationship to oxygenation. MAP is the pressure within the airway during a single respiratory cycle

[40]. Increases in oxygenation are directly related to increases in MAP and higher MAP is required when compliance of the lung is low, such as infants with respiratory decompensation. A decrease in MAP has been used in evaluating prophylactic surfactant in the treatment of RDS [41, 42]. As MAP and FiO_2improve the RSS scores are lowered showing an overall improvement.

The Ventilatory Index (VI) is an indicator of oxygenation and is similar to the oxygen index. Several studies looking at initial and secondary surfactant treatment and respiratory severity have defined VI as FiO_2 X MAP/PaO_2) [19, 37, 43, 44]. These took into consideration both MAP and FiO_2 but required arterial blood gas analysis to obtain the PaO_2 [19, 37, 43, 44]. These studies used the term VI as an indicator of oxygenation [44] All of these studies found an improvement in VI after surfactant dosing. The higher the VI the poorer the ventilation achieved. The VI has been used to look at pulmonary severity but is not considered as accurate as looking at PCO_2 and PIP [45, 46]. Peak inspiratory pressure is the primary factor used to deliver tidal volume on ventilated neonates. Respiratory rate is one of the primary determinants of minute ventilation. High frequency ventilation allows for high rates and low PIP to reduce trauma to the lungs. A modification of the VI (MVI) analyzes the PIP, PCO_2 and rate [PCO_2x PIP x RR/1000] [47, 48]. The MVI has been used in congenital diaphragmatic hernia (CDH) research to predict prognosis. These studies looked at the MVI in relationship to lung injury secondary to mechanical ventilation and showed that higher scores were predictive of higher mortality [49, 50]. One study was able to show that MVI was more predictive of outcome than PCO_2 alone and stated it was the most powerful predictor of survival followed by a lower PCO_2 [51]. These studies showed through multivariate analysis that

both MVI and PCO_2 were statistically significant and independent predictors of survival[50]. One study looking at MVI in the prognosis of surgical patients did not find any prognostic value [48]. Some of these studies defined the MVI as: [Peak Inspiratory Pressure (PIP) x RR][50]. Others define it as the [PIP x PCO_2x VR] divided by 1,000 [48, 52-57]. There is very little research in the literature on the use of the index other than in these patients.

The Ventilatory Efficiency Index (VEI) is an indicator of efficiency of CO_2 elimination [58]. The VEI was used to allow for a direct comparison of PCO_2 with changes in the ventilator. The VEI is defined as alveolar ventilation (VA) divided by the difference in ΔP (PIP – PEEP), multiplied by the frequency of the ventilator. Alveolar ventilation is the ratio of carbon dioxide (CO_2) production to the mole fraction of alveolar PCO_2 [VA =3800/PaCO2 where 3800 is a constant so that when used in the formula VEI = 3800/[PIP – PEEP] x VR x PaCO2 and is an indicator of CO_2 elimination [44, 58-60]. This index allows comparison of respiratory status when both ventilator pressures and PCO_2 values vary [58, 61]. It also allows for a measurement of changing lung function over time since VEI will increase as pulmonary function improves. There is no research looking at VEI in infants on High Frequency Ventilation (HFV).

All three of these scores have been used to assess respiratory severity in patient. They take into account pulmonary dynamics and changes in both respiratory status and ventilator settings. Infants with secondary surfactant dysfunction and deficiency may have underlying lung injury. The use of surfactant may improve the severity allowing some improvement in ventilator pressures and oxygen needs while the lungs heal.

SURFACTANT REPLACEMENT AND OUTCOMES IN ARDS

Surfactant replacement studies have been done in both animals and humans looking specifically at ARDS caused by aspirations and pneumonia. Animal studies using surfactant therapy in ARDS have demonstrated significant improvements in oxygenation and pulmonary function [62-64]. Pathology studies in ARDS have found diffuse alveolar damage, neutrophils, macrophages, erythrocytes, hyaline membranes and edema in the alveolar space and disruption in the alveolar epithelium similar to infants with RDS. Studies on adults with ARDS haves shown that natural surfactant replacement improves gas exchange and increases oxygenation [65-70]. Despite these studies a 2004 Cochrane review showed no effect on early mortality in 9 randomized controlled trials looking at secondary surfactant for ARDS [71]. Study data could not be pooled and no other comments related to outcomes could be made. Surfactant replacement trials are currently being done in infants and children. These studies have all shown improvement in both lung compliance and oxygenation and are summarized below.

HUMAN RESEARCH: OLDER INFANTS AND CHILDREN

Surfactant studies in pediatrics have been mostly case studies or small series research. Perez-Benavides treated seven children with severe ARDS and showed a rapid improvement [72]. Perez-Benavides in 1995 published their research looking at ARDS in pediatric patients after the administration of artificial surfactant (Exosurf) [72]. Seven patients ranging from 11 months to 10 years of age who were admitted to the pediatric intensive care unit with ARDS were given artificial surfactant. A retrospective analysis of five patients with ARDS was used as the control group. Although surfactant therapy did not appear to improve mortality in this group, there was a statistical significant improvement in their pulmonary dynamic compliance with no difference in mortality in

the surfactant treated children. These patients also stabilized earlier allowing for decreased ventilator support.

A case study by Moreno [73] in 1996 showed clinical improvement in a 6 week old neonate who received surfactant after developing RSV-induced ARDS. The infant had a history of prematurity but had no respiratory pathology in the neonatal period. Within 48 hours after intubation, there was progressive deterioration in the infant's respiratory status, and despite the use of high ventilator settings and nitric oxide, the infant continued to deteriorate. The decision was made to administer a porcine-minced lung surfactant (Curosurf). After the second dose of surfactant the infant had a dramatic improvement in oxygenation, with an increase in PaO_2 from 56 mmHg to 114 mmHg. This improvement continued with subsequent doses of surfactant, which allowed for a rapid reduction in ventilator settings. The infant received a total of 4 doses of Curosurf, over a 36 hour period of time.

A study by Lopez-Herce and colleagues in 1999 looked at the efficacy of surfactant in acute respiratory distress syndrome in infants and children [74]. Twenty patients from 1 month of age to 16 years with ARDS due to acute systemic, pulmonary or cardiac disease were treated with up to 6 doses of surfactant. Patients with systemic or pulmonary diseases showed a significant improvement in oxygenation, with an increase in PaO_2/FiO_2 ratio by 20% and a significant decrease from 36.9 to 27.1 in the oxygen index (OI) [(mean airway pressure x FiO_2/PaO_2], beginning with the first dose administered. Improvement was seen between 30 minutes and 4 hours after surfactant administration, with 75% of the patients showing improvement within the first hour after treatment. There was no significant difference seen in the PaO_2/FiO_2 ratio or OI in infants with

ARDS due to cardiac disease. They were able to show that surfactant leads to moderate improvement in children with ARDS.

Wilson in 1996 reported the results of a multicentered trial involving six pediatric intensive care units[56]. The study was an uncontrolled, observational study and utilized a convenience sample. Twenty-nine patients, between the ages of 1 month and 16 years were given surfactant (Infasurf) for acute hypoxic respiratory failure. Ten of the children were under six months of age. Retreatment with Infasurf was allowed at any time between 8 to 24 hours if criteria were met, up to a total of four doses. Twenty-four out of the 29 patients had an immediate improvement in oxygenation, ventilatory index and a decrease in ventilator support. The complications included air leaks in three patients and three episodes of hypoxia with dosing. Mortality rate was 14% compared to 72% and 87% reported by DeBruin in1992 and Timmons in1995 respectively [75, 76]. In a second randomized controlled trial by Wilson and colleagues, 42 children treated with surfactant for ARDS showed a rapid improvement in oxygenation and a decrease in ventilator days and length of stay in the PICU with no difference in mortality [77].

Acute respiratory distress syndrome (ARDS) frequently develops in children after infections, pneumonia's, shocks, burns and trauma [45]. Yapicioglu, et al in 2003 published the results of a prospectively designed study investigating the efficacy of surfactant in 12 children treated with surfactant for ARDS [45]. These children were between 5 and 10 years of age and received up to two dose of surfactant intratracheally. They analyzed VI defined as $PaCO_2$ x PIP x Respiratory rate/ 1000 and found a significant improvement in children treated with surfactant. These children had a

significant improvement in oxygenation and ventilation post surfactant dosing with a decreased need for ventilator support and an increased survival time.

Hermon and colleagues looked at surfactant replacement in seven older children (median age 9 months) who had ARDS [78]. There was a significant decrease in oxygenation index and the hypoxemia score. They found that a single dose of surfactant improved pulmonary function but that the second dose did not show further benefit. In a randomized, controlled trial by Tibby and colleagues, 19 ventilated infants with respiratory syncytial virus were randomized to either surfactant or placebo [57]. The OI and VI were evaluated in this study as an indication of gas exchange. Infants with an OI less than 5 or VI less than 20 were excluded from the study. Both OI and VI transiently increased with surfactant dosing but then decreased. OI decreased in both the surfactant treated and control group with the surfactant group having a more rapid drop. VI decreased significantly in the surfactant group. Infants in the surfactant group had a significant improvement in both oxygenation and ventilation.

Infants and children with ARDS have profound hypoxemia and respiratory failure. The incidence of ARDS in the pediatric population has been reported to be 0.8 to 4.4% with a mortality rate of 50-60% [75, 79]. Studies in older infants and children are showing significant improvement in respiratory severity, oxygenation and ventilation, however these studies are small. The evidence is apparent that larger, randomized controlled trials are needed to prove surfactant is effective and improves outcomes in neonates, infants and children with ARDS. Further trials will continue to increase knowledge and improve the therapeutic strategies in secondary surfactant therapy.

SIGNIFICANCE OF SECONDARY SURFACTANT DYSFUNCTION IN TERM AND PRETERM INFANTS

Surfactant therapy has been used to treat term infants with respiratory disorders other than primary surfactant deficiency, including meconium aspiration syndrome [80-83], pneumonia [84, 85], pulmonary hemorrhage [86-88], early chronic lung disease [61], respiratory failure[22, 80, 89, 90], RSV [73] and Group B Streptococcal infection [91, 92]. Lotze and colleagues, 1993, studied 56 term infants with respiratory failure requiring extracorporeal membrane oxygenation (ECMO). This was a blinded, randomized, controlled study with random assignment to surfactant or no surfactant while on ECMO. They found improved pulmonary mechanics, an increase in surfactant protein A content in tracheal aspirates, improvement in disease state and a decrease in time on ECMO [22]. A second multicentered study of surfactant use in term infants with meconium aspiration syndrome (MAS), sepsis or idiopathic persistent pulmonary hypertension of the newborn (PPHN) demonstrated a decrease need for ECMO in the group of infants who received surfactant therapy [80].

Premature infants have decreased amounts of surfactant as compared to the term infant and their surfactant is more susceptible to inactivation by inhibitors and by plasma dilution of the hypophase (thin layer of fluid and surfactant covering lung epithelium) [93]. Premature infants may recover from their primary respiratory distress syndrome only to develop a secondary surfactant dysfunction with an acute lung injury such as ARDS. This may in turn lead to atelectasis and the increased need for mechanical ventilation posing a risk of volutrauma or barotrauma to the immature lung with resulting prolonged ventilator exposure and BPD. Damage to the type II pneumocytes in the lungs leads to surfactant deficiency.

Odita in 2001 reviewed chest radiographs of 94 infants with the diagnosis of RDS who were treated with surfactant [94]. Thirty four infants had radiographic evidence of clearance of RDS within 3 days of initial surfactant treatment (mean gestational age 32.6 weeks). Twenty nine infants failed to respond to surfactant as measured by no radiographic improvement (mean gestational age 25.4 weeks). Thirty one of 34 infants had initial improvement in radiographs, but developed recurrent lung opacities within 10 days after the initial improvement from RDS (mean gestational age 27.7 weeks). Importantly, the group with recurrent opacities had a significantly higher incidence of BPD (72%) than the group that had no radiographic response to surfactant (50% BPD).

Sobel (1994) also investigated premature infants who initially responded positively to surfactant but had subsequent respiratory deterioration [95]. These infants also developed lung opacities on chest radiographs and had an increased incidence of BPD. The incidence of BPD was higher in these infants that developed lung opacities following initial surfactant therapy. The etiology of the secondary respiratory decompensation is multifactorial and may include inflammation due to aspiration, lung edema from barotrauma or patent ductus arteriosus, atelectasis, or infection.

Harms and Herting (1994) published a report of two former premature infants (24 and 26 weeks gestation at birth) diagnosed at three and twelve weeks of age with ARDS, as a consequence of chlamydial pneumonia [84]. Both infants were treated with surfactant (Survanta) and within 2 hours after administration, there was an improvement in $Pa0_2/FiO_2$ ratio and a decrease in the PIP required. Both infants were treated with an additional dose of surfactant (Survanta) ten hours later and survived without developing chronic lung disease.

A pilot study by Pandit (1995) reported on ten premature infants between 7-30 days of life, who were receiving oxygen and had diffuse haziness on chest radiographs [61]. They were given a single dose of surfactant to evaluate the effect on oxygenation and ventilation. There was a significant decrease in the oxygen requirement after therapy, which was sustained for 24 hours. Oxygen requirements increased after this time, but remained significantly lower than that required prior to treatment. There was also a trend toward improvement in ventilation [61].

In one pilot study 28 term and preterm infants with pneumonia, meconium aspiration or RDS were given 1-3 additional surfactant doses [96]. These infants were less than 4 days of age and were placed on HFJV for clinical deterioration after initial surfactant therapy. Only the 13 preterm infants in the study showed significant improvement in ventilatory and blood gas parameters with secondary surfactant administration while on HFJV.

Merrill and colleagues (2004) studied the effects of two secondary doses of surfactant on extremely low gestational age infants who remained ventilated at 7-10 days of age [97]. They also studied infants with respiratory deterioration at 5-21 days of age and the effects of up to two secondary doses of surfactant. Thirty-one extremely low birth weight infants qualified for secondary surfactant. These infants tolerated dosing and had a significant improvement in their respiratory severity scores. They concluded that secondary surfactant administration in ventilated low gestational age infants improves respiratory status [97].

A recent study by Katz and Klein (2006) evaluated repeated surfactant dosing in retrospective cohort of extremely low birth-weight patients over a 3 year time frame [98].

They defined respiratory failure after 6 days of age as postsurfactant slump. Twenty-five patients required secondary surfactant dosing after treatment from RDS and 70% of these patients showed a significant improvement in both lung disease and respiratory severity. They stated that a repeat course of surfactant for postsurfactant slump was beneficial on a short term basis.

As with ARDS patients, premature infants may develop acute lung injury and damage to the surfactant system. These secondary episodes of acute lung injury carry significant risk for the preterm neonate struggling to develop respiratory competence. Premature infants who have a respiratory decompensation from pneumonia or sepsis are at risk for surfactant dysfunction due to injury to the Type II alveolar cells. Atelectasis, capillary leak of fluid and protein, alveolar inflammation, and the release of inflammatory mediators may cause surfactant inhibition and contribute to the development of BPD in premature infants.

Mechanical ventilator pressures and the resulting volutrauma causes elastosis and fibrosis at the gas exchanging units and alveolar ducts [99]. Particularly important is the deposition of collagen and elastin that leads to dramatic structural changes seen in BPD. An increase in saccule diameter and alveolar septal thickness is a result of the ongoing inflammation in BPD. Although secondary surfactant deficiency or inhibition may not be the sole determinant of the damage seen with BPD, surfactant administration during secondary insults may acutely improve pulmonary function and help mitigate the inflammatory cascade. Limited case studies have demonstrated a positive response to surfactant administration in infants and children who have had clinical evidence of SSD or ARDS.

All of these studies solidify the need for further research to evaluate the efficacy and safety of administering surfactant in neonates with clinical conditions who may have a component of secondary surfactant deficiency. Alternative therapies that acutely improve compliance and decrease barotrauma, volutrauma, and ventilatory requirements are limited. Commonly used therapies of lasix and dexamethasone have well known risks of electrolyte disturbances, metabolic alkalosis, nephrocalcinosis, hypertension, poor growth (catabolism) and poor long-term neurological outcome. A second round of surfactant therapy in neonates with ARDS-type insults may offer significant short-term benefits to lung compliance as well as decreasing the ventilatory requirements by improving pulmonary function. Long term benefits may involve fewer days of mechanical ventilation and shorter hospital stays. Surfactant administration may also help minimize use of other therapies that have more worrisome side effects.

PRELIMINARY STUDIES

Case Study

A retrospective, descriptive case series was completed on 3 premature infants who had received 1-2 doses of Infasurf (Forest Laboratories, Inc.) between 13 and 18 days of life for an acute respiratory deterioration and after initial surfactant treatment for RDS [100]. Blood gases and ventilatory settings were reviewed before and after the secondary surfactant administration. Chest radiographs were reviewed and interpreted by pediatric radiologists who were unaware of the secondary surfactant dosing.

Baby girl A was born at 26 weeks gestation, 835 grams and was given Infasurf on DOL 14 for respiratory decompensation with marked respiratory acidosis and the need for high frequency oscillatory ventilation (HFOV). The chest X-ray (CXR) prior to dosing showed diffuse bilateral airspace disease consistent with pneumonia. One dose of

surfactant was administered 2 hours after being placed on HFOV, with improvement in pCO2 to the 40's. She was weaned to conventional ventilation within 15 hours. The repeat CXR 24 hours later showed improved aeration. This infant again decompensated on DOL 16, requiring the use of high frequency jet ventilation (HFJV) with an end-expiratory pressure of 9. The infant continued to worsen despite HFJV, and on DOL 18 received a second dose of surfactant. The infant subsequently weaned on HFJV to conventional ventilation within 24 hours and the CXR expansion improved, from low lung volumes with diffuse disease, to mild hyperinflation 24 hours later. She did not receive steroids or respiratory inhalants before or during secondary surfactant dosing, but had been on daily furosemide since DOL 9.

Baby Boy B was born at 24 5/7 weeks gestation, 695 grams and was given Infasurf on DOL 17 for respiratory decompensation following presumed infection and pneumonia. The chest X-ray prior to dosing showed a marked worsening aeration with almost complete opacification on the right and diffuse lung disease on the left. The infant received 2 doses of surfactant 14 hours apart with a dramatic drop in pCO2 with surfactant administration while the ventilator rate and FiO2 were also decreasing. Within 48 hours of dosing, the infant was extubated to CPAP. The follow up CXR 24 hours after the first dose, showed improved aeration with minor atelectasis in the right lower lobe and bilateral diffuse lung disease. The infant did not receive steroids, diuretics or respiratory inhalants before or during secondary surfactant dosing.

Baby Girl C was born at 26 weeks gestation, 720 grams and was given Infasurf on DOL 11 secondary to respiratory decompensation with an inability to oxygenate on conventional ventilation and a subsequent change to HFJV. The infant initially responded

well to HFJV on an end expiratory pressure of 6 with improvement in oxygenation but went on to develop significant CO2 retention over the next 12 hours. CXR prior to dosing showed increased opacifications bilaterally. An echocardiogram completed at that time showed no PDA. On DOL 12, the infant received 1 dose of surfactant with a decrease in PCO2 within 1 hour of dosing. HFJV was quickly weaned to conventional ventilation, with continued weaning of FiO2, peak inspiratory pressures and rate over the next 12 hours while arterial blood gases (ABGs) were improving. At 24 hours after surfactant both oxygenation and ventilation began to worsen, but the infant did not receive additional doses. The CXR at 24 hours showed increasing opacification consistent with pneumonia. The infant did not receive diuretics, respiratory inhalants or additional steroids during the course of secondary surfactant treatment.

A few studies have demonstrated a positive response to secondary surfactant administration in infants and children who have had clinical evidence of respiratory failure [74, 84, 91]. Our case series also reports favorable short term improvements in multiple ventilatory and blood gas parameters in neonates between 1-3 weeks of age with secondary surfactant administration.

Pilot Study

A prospective pilot study was performed by Bissinger and Carlson to study the effects of secondary surfactant administration on oxygen and ventilatory requirements of neonates who had respiratory decompensation after recovery from primary RDS. Entry criteria included infants admitted with RDS who were 7 days to 3 months of age, with birth weights greater than or equal to 500 grams. Infants then qualified if they demonstrated recovery from RDS with a secondary respiratory decompensation defined prospectively as an acute pulmonary decompensation after 6 days of age, which was non-

cardiac in origin and accompanied by diffuse parenchymal lung disease on chest x-ray, in conjunction with sustained increase in fraction of inspired oxygen (FiO_2; $\geq 20\%$) and mean airway pressure (MAP; ≥ 2 cm) above base-line for at least 4 hours prior to surfactant administration. Infants meeting all entry criteria received surfactant within four hours of the qualifying decompensation and again 12 hours later. Two surfactants were used for the study (Curosurf and Survanta) and infants were assigned on an alternating basis. Oxygen and ventilatory requirements were compared before and after administration at 2, 12 and 24 hours.

Twenty neonates qualified for secondary surfactant administration. Mean values (range): birth weight, 813 g (520-1200 g); gestation, 25 weeks (24-29 weeks); and postnatal age at study entry, 20 days (7-77 days). The PCO_2, pH, MAP and FiO_2 all improved significantly at 12 and 24 hours after surfactant administration. This improvement was maintained in all patients during the 24 hour period. Infants who received Curosurf had noted improvement in pH and PCO_2 within 2 hours of surfactant administration. The rates of adverse events were low (desaturations with dosing), and no serious adverse events were documented. X-rays were read by the pediatric radiologist in a blinded fashion with improved aeration noted on 50% of the x-rays.

These findings suggest that secondary surfactant administration may be effective in reducing short term oxygen and ventilatory requirements in neonates who have a respiratory decompensation after recovery from initial RDS. Secondary surfactant replacement may improve outcomes in this subset of patients and further randomized controlled trials are needed to confirm these preliminary findings. Changes in PCO_2, pH, MAP and FiO_2 can all be influenced with changes in ventilator changes. To further

analyze the data and assess the significance of these findings respirator severity scores and other indicators of ventilatory efficiency need to be analyzed.

THEORETICAL FRAMEWORK

The question of whether there is a secondary surfactant deficiency or surfactant dysfunction in premature infants is beginning to be studied and addressed in the literature. The conceptual model below uses the proposed pathogenic sequence of events proposed by Lewis and Jobe in 1993 and Jobe and Ikegami in 1998 and expands on this model to include surfactant replacement and pulmonary improvement[13, 101]. Lewis and Jobe (1993) summarized the role of altered surfactant in describing the pathophysiology of ARDS and continued to develop this model looking at inflammation, type II pneumocytes, alveolar capillary integrity and surfactant metabolism. This model was expanded to include surfactant replacement and pulmonary improvement to guide the research [101]. This model helps explain and predict the cause of secondary respiratory failure leading to SSD and response from secondary surfactant dosing.

There is a precipitating lung injury, either a direct injury to the lung or an indirect injury secondary to systemic disease. As previously stated the direct injuries are commonly caused by pneumonia, aspiration of gastric contents, near-drowning, inhalation injury and reperfusion injury. Common indirect causes include sepsis, as the highest risk and severe trauma with shock [102].This lung injury can precipitate surfactant deficiency or dysfunction through 3 processes: Alveolar capillary damage, Alteration of type II pneumocytes and Inflammation of cell activation. Alterations in surfactant function lead to problems with lung mechanics and gas exchange with resultant respiratory failure.

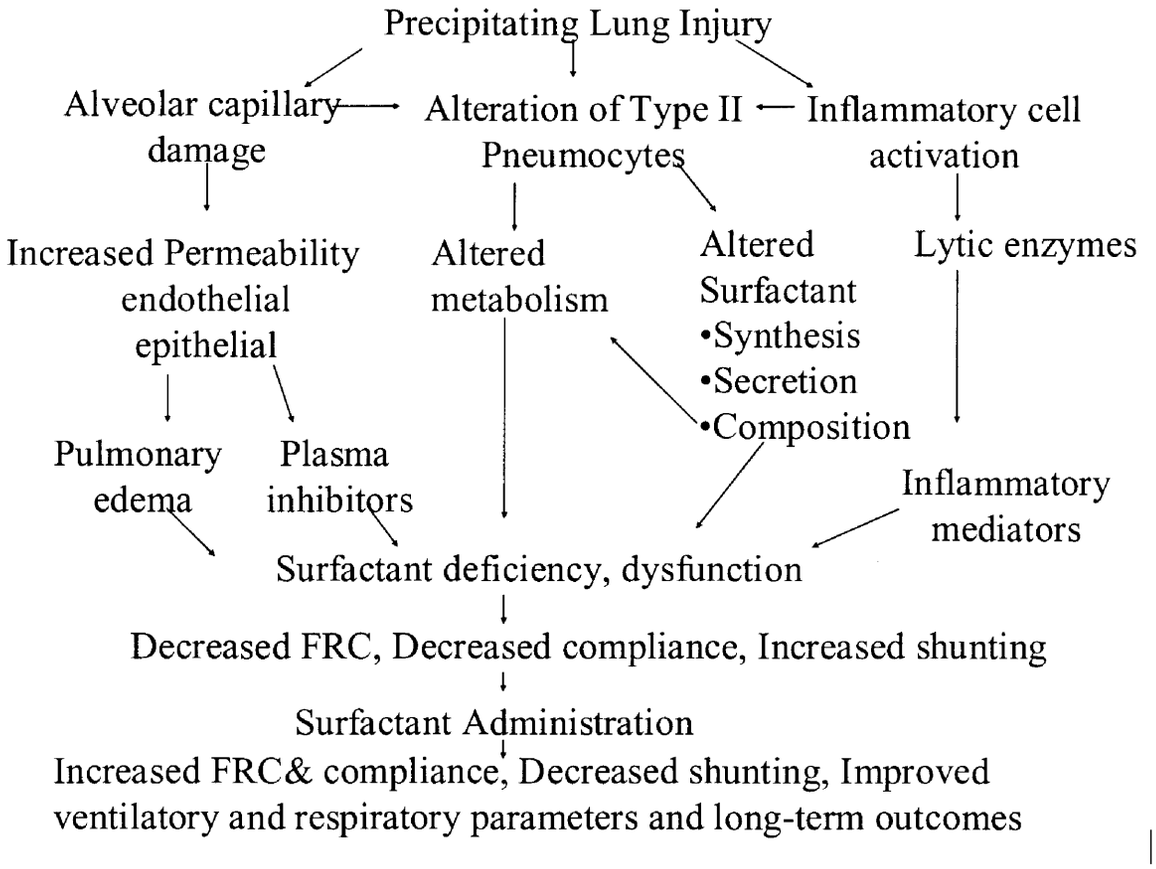

FIGURE 1: Sequence of Events in Surfactant Dysfunction and Deficiency.

The alveolar capillary barrier is made up of the microvascular endothelium and the alveolar epithelium. Capillary alveolar damage leads to an increase vascular endothelial and alveolar epithelial permeability leading to pulmonary edema with an influx of plasma inhibitors. Pulmonary edema and changes in surfactant metabolism can lead to surfactant dilution and inactivation of surfactant. Blood proteins, fibrinogen, lipids and cholesterol in the alveolar fluid interact with surfactant, inhibiting its activity and impairing surface activity with a subsequent increase in surface tension. Plasma and blood proteins absorb and block the air water interface, also inhibiting surfactant activity. Alveolar capillary damage can also lead to alterations in Type II pneumocytes leading to alterations in surfactant metabolism and the formation of abnormal surfactant aggregates.

Type I cells make up 90 % of the alveolar surface and the cuboidal type II cells make up the remaining 10%. Type II cells are more resistant to injury than the Type I cells.

With lung damage type II cells de differentiate into type I cells. Surfactant is continuously synthesized and recycled in the Type II cells. Damage to Type II alveolar cells leads to alterations in the synthesis, secretion, recycling and quantitative or qualitative composition of surfactant being produced and alters the metabolism leading to surfactant deficiency. Alterations in surfactant activity result in further surfactant dysfunction [10, 101, 103]. Surfactant can be removed from the functional pool in the alveoli by the formation of hyaline membranes.

Surfactant may be damaged or inactivated by enzymes or inflammatory mediators found in plasma proteins that leak into the alveoli. Damaged Type II pneumocytes secrete small surfactant aggregates which have depleted or altered phospholipids and protein content leading to decreased surface activity. Phosphatidylinositol and spingomyelin are increased with decreased amounts of phosphatidylglycerol and saturated phosphatidylcholine leading to alveolar instability and decreased pulmonary compliance [13]. Metabolism and function of surfactant is affected by this change in composition. Alterations in the phospholipids profiles area an indication of abnormal surfactant metabolic pathways [101]. In addition, damage to Type II alveolar cells can alter or destroy surfactant or prevent recycling of surfactant. Injury to Type II cells impairs the removal of edema from the alveolar space. Edema and inflammation inactivate surfactant. Alveolar filling may be increased from the pulmonary edema and/or atelectasis from surfactant dysfunction leading to a decrease in the functional residual capacity and compliance and increased ventilation-perfusion mismatch [13, 101]. Edema, inflammation and injury lead to the formation of hyaline membranes with the

deposits of fibrin and debris. Even with surfactant replacement there may be delayed clearance of fibrin from the alveoli in complex lung injuries [101].

Lung injury leads to inflammatory cell activation. Lytic enzymes cause chemical degradation and along with reactive oxidants degrade and alter essential phospholipids which reduces surfactant surface activity and increases surface tension. Degradation of phospholipids leads to an increase in lysophospholipids and free fatty acids. These enzymes cause biochemical degradation of the surfactant proteins. This changes the functional ability of surfactant. Release of inflammatory mediators will increase the production of substances that promote local systemic inflammation. Early response cytokienes include TNF alpha and Interleukin (IL) 1. IL 6 and IL8 are released through neutrophil activation. Inflammatory mediators affect the activity of surfactant through damage to surfactant phospholipids and proteins and alteration of the function of type II cells in surfactant synthesis.

Abnormalities in lung mechanics and gas exchange with lung injury may be explained by surfactant deficiency or dysfunction. An alteration in surfactant synthesis and recycling depletes surfactant stores. Further inhibition and inactivation of surfactant precipitates respiratory failure. Alveolar instability leads to a decrease in functional residual capacity resulting in the collapse of alveoli and subsequent atelectasis with bilateral alveolar infiltrates on X-ray. Decreased compliance with increased surface tension increases the infants' work of breathing or respiratory effort requiring increased ventilatory support and oxygen. Surfactant deficiency and dysfunction lead to intrapulmonary shunting with further ventilatory/perfusion mismatch and hypoxia. Hyperoxia leads to further lung injury. Infants in respiratory failure often require 85-

100% oxygen which can kill type II cells. A high level of oxygen leads to the production of oxygen free radicals and increases the presence of inflammatory mediators, further worsening surfactant synthesis and function. The need for mechanical ventilation at high pressures and volumes due to the cyclic opening and closing of atelectatic alveoli can cause lung injury (barotraumas and volutrauma) and worsen the inflammatory cascade within the lung [104]. Secondary surfactant administration in these infants may improve FRC and compliance and decrease intrapulmonary shunting as evidenced by improvement in ventilation, oxygenation and pulmonary function.

MANUSCRIPT ONE

SURFACTANT

Introduction

Swiss physiologist, Kurt von Neergaard was the first to publish the concept that respiratory distress in premature infants was due to the absence, not the presence of something (1). His paper in 1929 outlined the retractile forces of the lung and the dependent surface tension in the alveoli which led to a huge body of research describing the composition, metabolism and role of surfactant (1). Surfactant deficiency was later identified in 1959 by Avery and Mead who demonstrated decreased amounts of surface active properties in the lung extracts of infants who died of Respiratory Distress Syndrome (RDS) compared to infants who died of other causes (2). Over the last 20 years, surfactant replacement therapy has contributed to a decrease in mortality and morbidity in premature infants with RDS. It has changed the management of RDS in the Neonatal Intensive Care unit, improved outcomes and is beginning to be used with other neonatal respiratory diseases.

Surfactant Composition, Metabolism and Function

The composition, metabolism and function of surfactant have been studied extensively with several published reviews and symposiums (3, 4, 5, and 6). Surfactant is a complex phospholipid produced and secreted by the Type II alveolar cells in the lung. It is synthesized and recycled through complex metabolic pathways. Surface active properties decrease the surface tension at the air-water interfaces in the alveoli, preventing collapse during the entire respiratory cycle (4, 6, 7). Surfactant also plays a

role in host defense and improves mucociliary clearance with removal of particles from the lungs (6,8).

Surfactant is composed of 6 phospholipids and 4 apoproteins. The components of surfactant are 80-86% phospholipids, 8% neutral lipids and 6-12 % proteins (3,9,10). Saturated phosphatidylcholine (PC or lecithin) accounts for 70% of the phospholipid portion of surfactant, with dipalmitoylphosphatidylcholine (DPPC) accounting for 60% of the phosphatidylcholine (3). This disaturated phospholipid, DPPC, is critical for lowering the surface tension and can reduce it to almost zero (3). Although DPPC is the primary component for surface activity, alone it adsorbs poorly to the air-liquid interfaces within the alveoli. The presence of the surfactant proteins and other unsaturated phospholipids aid in the adsorption and surface active properties of surfactant (3). The amount of DPPC in the lungs is dependent on lung development, with an increase seen at 22 weeks gestation (3). Sphingomyelin is a phospholipid seen in inverse proportions relative to phosphatidylcholine, with levels of sphingomyelin decreasing with lung maturity. The ratio of lecithin (phosphatidylcholine) to sphingomyelin is used to determine lung maturity.

Phosphatidylglycerol (PG) and phosphatidylinositol (PI) are acidic phospholipids that aid in DPPC adsorption, with the amounts of each of these substances affected by lung development and lung injury. They account for about 10% of total lipids (6). During initial surfactant development in the fetus, phosphatidylinositol is the primary acidic phospholipid, with increases of phosphatidylglycerol seen in the more mature lung after 34-35 weeks gestation (3,11). The presence of PG in the amniotic fluid is an important determinate of lung maturity.

As with phospholipid composition, the protein content of surfactant has been identified through lung lavage or minced lung extract. There are 4 unique surfactant apoproteins (SP-A, SP-B, SP-C and SP-D) that have been identified in extracted lung fluid. SP-A and SP-D are hydrophilic, related to the collagenous lectins (colletins) and while not critical to surface activity are involved with down- regulating the inflammatory response of the lung (3,7,8). SP-A, discovered in 1972, accounts for the majority of surfactant proteins and functions as a host defense molecule in the alveoli, interacting with the immune cells of the lungs (3). It binds endotoxin as well as a wide range of gram-positive and gram-negative organisms and promotes phagocytosis by alveolar macrophages (3,6). In the presence of SP-B and SP-C, it plays a major role in promoting the adsorption of surfactant phospholipids at the air-liquid interface. SP-A plays a key role in the regulation of secretions and recycling of surfactant by alveolar Type II cells and increases the resistance to surface inhibition (12). SP-D is similar to SP-A in structure and function, binding bacteria and fungi (3). Although it does not play a role in surface activity, SP-D plays an important role in phospholipid homeostasis and in lung defense against bacteria, fungi and viruses (8,10). SP-B and SP-C are hydrophobic proteins that improve the surface activity of surfactant phospholipids and are thought to be a critical component of natural surfactants. Both of these proteins are important for the rapid spreading and adsorption of phospholipids onto the alveolar surface. SP-B, along with SP-A is essential for tubular myelin formation and along with SP-C promotes the adsorption of DPPC (3,4,7). SP-B is critical for the stability of surfactant and due to this stabilizing ability, a SP-B deficiency is fatal in infants.

The process of surfactant metabolism and re-cycling is complex. There are 2 types of alveolar cells. Type I cells are the gas exchanging units and Type II cells are responsible for surfactant synthesis and release. Precursors of surfactant are carried to the epithelial cells via the circulatory system and enter by diffusion through the capillary endothelium. After passage through the Golgi complex, synthesis of dipalmitoylphosphatidylcholine (DPPC) takes place in the endoplasmic reticulum of the Type II alveolar cells (1). The DPPC and hydrophobic proteins SP-B and SP-C are packaged with the lamellar bodies, the storage and secretory granules within Type II cells. This accounts for the intracellular pool of surfactant (6). Once secreted into the hypophase (a thin fluid layer covering the distal epithelium of the lung), the lamellar bodies, along with SP-A and calcium unravel to form the large aggregates of tubular myelin (1,3,4). Tubular myelin is a rich lipid material made up of monolayers and contains all surfactant components (6). Layers of phospholipids including DPPC, unsaturated PC and PG are released from the tubular myelin at the air-liquid interface and along with the surfactant proteins spread on the surface of the alveoli, forming a film between the alveoli and capillaries which will reduce surface tension. This bipolar monolayer of phospholipid molecules is dependent on the small apoproteins (SP-B and SP-C), to maintain stability during the respiratory cycle. During exhalation there is a reduction in surface tension and the monolayer becomes enriched with DPPC, with inhalation and alveolar expansion, there is release and re-spreading of the surfactant (3,10). About 90-95% of the surfactant is recycled and reprocessed into the Type II alveolar cells for re-secretion (3,7). This is a dynamic process, and with the surface area changes during the respiratory cycle, there is continual turnover of surfactant at the alveolar level. There are differences in the size and

functional role of these surfactant aggregates, with the large aggregates being the surface-active portion of surfactant and the precursors of the surface film at the air-liquid interface in the alveoli. Once these large aggregates are used up, small aggregates with no surface active properties and lesser amounts of the surfactant proteins appear in the alveolus (13). Surfactant is then either cleared from the lungs or recycled back into the lamellar bodies.

The most important physiological function of surfactant is the effect it has on lung mechanics. By lowering the surface tension within the alveolus at the air-liquid interface, there is stabilization of lung volumes at low transpulmonary pressures. Surfactant will prevent collapse of the airways on expiration and allow for lower opening pressures to inflate the lung. Overall, there is less overdistension of alveoli, decreasing the risks of alveolar rupture as surfactant decreases the negative pressure needed to open the airways and the work of breathing (14). Surfactant promotes the gas exchange between the alveoli and capillaries, and plays a role in host defense mechanisms through the action of SP-A and SP-D. Adverse effects of surfactant therapy include transient decreases in blood pressure, cerebral blood flow velocity, oxyhemoglobin concentration and activity as well as an increase in intraventricular hemorrhage (9).

Surfactant Replacement Therapy

Research on surfactant composition has been extensive and clinical studies have been done to determine the amount, method of administration and timing of therapy in neonates with primary RDS. There are two types of exogenous surfactant products available. These are natural surfactants derived from animal sources and synthetic surfactants (see Table 1). These surfactant products differ in composition and the presence of surfactant-associated proteins. The early surfactant products were synthetic,

consisting only of phospholipids, specifically DPPC. These products were protein free, with various amounts of phospholipids, and limited beneficial effects. Pneumactant (ALEC®; Britannia Pharmaceuticals, UK) contained DPPC and PG, but there were difficulties initially in diluting the powder for administration, and the product was re-formulated. As of 2000, it is no longer available for clinical use (15). Colfosceril palmitate (Exosurf®; Glaxo Wellcome, USA), also a protein-free synthetic product containing DPPC, has been widely studied alone and in comparison with other surfactant products but is no longer available in the United States (16-22). The new generation of synthetic products includes Lucinactant (Surfaxin®; Discovery Labs Warrington, Pa.) and Recombinant SP-C surfactant (Venticute®; ALTANA Pharma AG, Konstanz, Germany). Surfaxin contains a synthesized peptide that mimics SP-B. Sinapultide or KL4 is the peptide in Surfaxin designed to imitate the actions of SP-B in lowering surface tension and facilitating oxygen exchange (23). Lusupultide is the recombinant surfactant protein C present in Venticute.

Natural surfactant products vary in the origin of lung material, with products containing either lung lavage extract or minced lung extract. Beractant (Survanta®; Ross Labs Columbus, Ohio), Poractant alpha (Curosurf®; Dey, Inc. Napa Valley, Ca) and surfactant TA (Surfacten®); Mitsubishi Pharma, Tokoyo, Japan), are examples of the minced lung extracts, derived from cows, calves or pigs. Calfactant CLSE (Infasurf®; Forest Pharmaceuticals, St. Louis, Mo.) and Bovine Lipid surfactant (bLES®; BLES Biochemicals Inc, London, Ontario, Canada) are derived from bovine lung lavage. In the United States, the current biological surfactants used in neonates with RDS include

Infasurf®, Survanta®, and Curosurf®. Natural surfactant from mammalian lungs has been shown to be most efficacious in treatment of neonatal RDS.

Surfactant: Natural	**Total Proteins**	**Total Phospholipids**	**SP-B**	**SP-C**
Survanta®	<0.5% 1.0 mg/ml	25mg/ml DPPC 50%, PG	0.01 mg/ml	0.99 mg/ml
Infasurf®	0.65 mg/ml	35mg/ml DPPC 53%	0.26 mg/ml	0.39 mg/ml
Curosurf®	1.0 mg/ml	80mg/ml DPPC 35%	0.3 mg/ml	0.7 mg/ml
Surfactant: Synthetic				
Exosurf ®	N/A	13.5 mg/ml 84.5% DPPC Hexadecanol (9.5%) Tyloxapol(6%)	No	No
Surfaxin®	KL4 (synthetic SP-B)	DPPC 75%		Synthetic SP-B protein analogue KL_4 (0.8mg)

Table 1: Composition of Natural and Synthetic Surfactants used in the United States

The most abundant phospholipid in the exogenous preparations of surfactant is dipalmitoylphosphatidylcholine (DPPC), with additional phospholipids, neutral lipids and fatty acids in smaller concentrations (15). Surfactant proteins, SP-B and SP-C, critical to the surface active properties and activity of surfactant are also found in preparations of natural surfactant. However, due to the purification process used in preparing surfactant, none of the currently available surfactant products contain the hydrophilic proteins SP-A or SP-D (9). The amount of phospholipids and surfactant proteins SP-B and SP-C varies in the exogenous surfactant products currently available. The phospholipid content of the

surfactant products ranges from 25 mg/ml to 80mg/ml (See Table 1). DPPC is the main component, with the addition of PG in Survanta and Surfacten. The lung mince extracts contain less that 10% of SP-B compared to what is found in the lung wash extracts (9). These variations in surfactant product composition may explain differences in clinical response seen in trials for RDS, and may be important in the treatment of other respiratory diseases in the future.

Surfactant Administration and Dosing

Surfactant administration has been studied using bolus, lavage and aerosolization. The majority of surfactant studies have used intratracheal bolus administration in divided doses and total volume of surfactant standardized by patient body weight for calculating the dose (11, 24-27). Bolus administration using a dual lumen endotracheal tube or catheter has been shown to be effective and may cause less adverse events (28). The use of a valve attached to the endotracheal tube which allows administration of surfactant without interruption of the mechanical ventilator has also been utilized. Early studies using aerosolized surfactant showed an inability to deliver an adequate amount to the lungs (29). Lavage therapy uses larger volumes of dilute surfactant in a "washing out" procedure, where surfactant is removed by suctioning at the end of the procedure (15).

Intra-amniotic administration of surfactant has also been studied. Women with spontaneous rupture of membranes between 24 and 32 weeks gestation were given aminophylline, a respiratory stimulant, and surfactant was administered close to the fetal nose and mouth, through an endoscope passed through the cervical canal during active preterm labor. There were no fetal or maternal complications, but the researchers were unable to demonstrate conclusively the distribution of surfactant to the distal airways (30,31). Nasopharyngeal administration of surfactant in preterm infants prior to the

delivery of the shoulders followed by mask continuous positive airway pressure (CPAP) has also been studied (32). Animal studies have suggested that delivery of surfactant to a fluid filled lung may allow for more uniform distribution. A small pilot study on preterm infants less than 30 weeks showed rapid weaning to room air with CPAP and decrease need for mechanical ventilation (32). The difficulties with this method of administration include infants with breech presentations and those born by Caesarean section. Further studies are needed.

Adverse events from administration include transient hypoxia and bradycardia because of the initial airway obstruction. Reflux of surfactant, increase in carbon dioxide levels, tachycardia, gagging and mucous plugging have also been reported (9). Slow administration and careful monitoring are essential. It is important to understand the specific recommendations for preparation and positioning for each of the different surfactant products. Lack of compliance and understanding of the differences in methods of warming, mixing and infant positioning may affect the physiologic properties of the surfactant product and therefore function. Preparation, administration and dosing can be found in product package inserts.

Surfactant Comparision

Distinct biochemical differences in the surfactants may play a role in different clinical responses to the drugs. The exogenous surfactants vary in composition and function from alveolar surfactant. The first generation of commercially available surfactants, lack many of the components of natural surfactants specifically the surfactant apoproteins. Numerous studies have shown differences in the activities of the surfactant replacement products in laboratory comparisons (33-36). The addition of SP-B showed a significant improvement in function. The first natural surfactant (animal-derived) was

reported in a non-randomized study in 1980 (37). Huge randomized control trials after this publication evaluated surfactant use for the treatment of RDS and found that it improved lung function and mortality (19). From these early studies, large randomized controlled trials for safety and efficacy were completed showing that surfactant therapy for RDS decreased mortality by 40% and reduced the occurrence of pneumothorax (1). Current studies have shown that all natural surfactants are superior to the first generation of synthetic products (38,39). These studies show an immediate response of the natural surfactants with improved oxygenation and lung compliance with a decrease in pneumothorax and mortality (9). There is also a more rapid onset of action with a rapid ability to wean the ventilator and oxygen concentration. This may be due to the lack of surfactant proteins, specifically SP-B in these older synthetic surfactant products. The delay in the effect of the first generation synthetic surfactants may be related to the process of recycling with clinical effects being seen after it combines with the infant's endogenous apoproteins.

The two newer synthetic surfactants, Surfaxin and Venticute are composed of totally synthesized components and contain synthetic proteins. As stated earlier, Surfaxin is prepared with a SP-B protein analogue and Venticute uses recombinant SP-C protein. Research on the safety and efficacy of Surfaxin has been done and further studies using Surfaxin in the treatment of RDS and Bronchopulmonary Dysplasia in premature infants and meconium aspiration syndrome in full-term infants are currently underway. Venticute which contains rSP-C has been studied in the treatment of Acute Respiratory Distress Syndrome (ARDS) in adult patients and in animal studies. Further studies are needed in both the pediatric and adult population, as well as the extremely low birth

weight premature infant. This new generation of synthetic surfactant replacement therapy holds promise for future use without potential infectious disease and immune implications.

There have been several randomized controlled trials comparing the natural surfactants. The first compared Survanta with Infasurf and the second compared Survanta with Curosurf (40, 41). In both trials, the Survanta treated infants had higher oxygen requirements and mean airway pressures at 24 to 48 hours after dosing. The Infasurf group showed a longer interval for dosing indicating a longer treatment effect. A meta-analysis of 5 studies was done comparing Curosurf and Survanta in the treatment of RDS (42). Curosurf which is recovered from minced porcine lungs contains SP-B, SP-C, and increased concentrations of total phospholipids as compared to Survanta. The results of this meta-analysis suggested that Curosurf may act more rapidly, have fewer complications related to dosing and improve survival when compared to treatment with Survanta.

The differences in the commercially available surfactants may be important when treating different disease processes with one surfactant being more beneficial compared to another due to its composition. In addition, there may be benefits with the administration of SP-A and SP-D, which have important roles in host defense as well as surfactant secretion and re-uptake (1). Future surfactant research will need to focus on the extremely low birth weight infant, as there may be developmental differences in the lungs that affect surfactant function. Currently there is no evidence that has established the superiority of one surfactant product over another (9).

Expanded uses for Surfactant

Surfactant activity can be affected by several factors; (a) through removal of surfactant from the functional pool in the alveoli with the formation of hyaline membranes, (b) damage or inactivation by enzymes or inflammatory mediators, (c) inactivation by plasma proteins in the alveolus, increased amounts of the smaller aggregates of surfactant with decreased surfactant protein activity and changes in phospholipid content, (d) alteration or destruction of the surfactant or lack of recycling of surfactant due to damage to the Type II alveolar cells, (e) loss of surfactant due to high volume ventilation (13,43). Surfactant therapy in the neonatal population for respiratory disorders other than the specific treatment of RDS is being investigated. The respiratory disorders include meconium aspiration syndrome (44), pneumonia (45), early chronic lung disease (46), respiratory failure (26,47-49), Respiratory Syncytial virus (49) and Group B Streptococcal infection (50). Surfactant has been shown to be inactivated in diseases such as meconium aspiration syndrome, pulmonary hemorrhage and conditions associated with increased pulmonary alveolar capillary permeability, such as pneumonia (51).

Surfactant activity is inhibited by proteins, bilirubin, free fatty acids, bile salts, triglycerides and cholesterol found in meconium (51, 52). These components decrease surfactant's ability to lower surface tension (52). Meconium also decreases production of SP-A and SP-B (15). Meconium aspiration syndrome (MAS) is characterized by chemical pneumonitis, mechanical airway obstruction and surfactant inactivation leading to decreased air exchange and lung compliance (25). Studies have shown that this inactivation of surfactant by meconium can be overcome with the addition of exogenous surfactant. Surfactant is also thought to improve mucociliary clearance by increasing

ciliary beat frequency and decreasing mucous viscosity (53, 54). With MAS the airways are often partially or completely obstructed making dose concentration and mode of delivery important. Studies have shown that larger doses are needed and that it often takes a second or third dose before improvement is seen (25, 44, 48). Lavage therapy may be more beneficial than bolus in MAS. The thick particulate meconium blocks the airways leading to atelectasis or hyperexpansion, ventilation perfusion mismatch and air leaks. Lavage therapy utilizes the detergent properties of surfactant in removing meconium and debris from the airway with a subsequent increase in alveolar surfactant, improving gas exchange (55-57). Surfactant administration, both bolus or lavage, in infants with MAS has been shown to reduce air leaks, decrease the need for extracorporeal membrane oxygenation (ECMO), and decrease the days on the ventilator, days on oxygen and length of stay (15, 51). Further research is needed to determine the timing, method and dosing of surfactant administration. SP-A and SP-B has been reported to be decreased in infants with MAS, which may also be important in deciding which type of surfactant would be most efficacious.

Surfactant may be altered by infections such as pneumonia and sepsis. Viral and bacterial pneumonias can affect both surfactant composition and function. Viruses have been shown to alter Type II pneumocytes (15). Lavage studies have shown abnormalities in both the lipid and protein composition of surfactant in patients who have pneumonia or infection (58, 59). The influx of plasma proteins from increased alveolar permeability inactivates surfactant (60). Several neonatal studies have shown that surfactant is beneficial in the treatment of pneumonia and bronchiolitis resulting in improved oxygenation, lung compliance and ventilation (45, 61-63). One study showed that

multiple doses of surfactant were significant but dosing appeared to be most valuable when initiated early in the treatment of respiratory distress because of the rapid improvement in oxygenation (48). Surfactant replacement therapy improves lung function and oxygenation and restores surface tension (64-66).

Pulmonary hemorrhage leads to hemoglobin and plasma in the alveoli that impairs the surface tension lowering properties of surfactant (15). A retrospective study looking at infants who received surfactant after a pulmonary hemorrhage showed improvement in ventilation and oxygenation (67). Pulmonary hemorrhage did not reoccur in these patients. A study by Seeger et al showed different sensitivities to fibrinogen, albumin and hemoglobin among different types of surfactants (36). Survanta and Curosurf activity were significantly inhibited by all levels of proteins studied, including fibrinogen, hemoglobin, and albumin (36). Infasurf activity was not affected by albumin or hemoglobin, and only moderately inhibited by high levels of fibrinogen (36). Surfaxin has been shown to have superior resistance to inactivation by oxidation and plasma components such as fibrinogen and c-reactive protein. This may prove to be beneficial in treating infants with pneumonia or pulmonary hemorrhage.

Premature infants may develop acute lung injury and damage to the surfactant system after recovery from their initial RDS, similar to ARDS. ARDS is a syndrome of acute lung injury seen in the pediatric and adult population, caused by a variety of insults to the lung (10). It is characterized by an acute onset of refractory hypoxemia with pulmonary edema, loss of lung volume, worsening lung compliance requiring high ventilatory pressures and diffuse alveolar infiltrates on chest radiographs (10,15). Secondary episodes of acute lung injury in neonates are multifactorial, including inflammation due

to aspiration or sepsis, lung edema from barotrauma or patent ductus arteriosus, pulmonary hemorrhage, or pneumonia. Surfactant inactivation or dysfunction can lead to this Secondary Surfactant Deficiency (SSD). The authors' case series reported that exogenous surfactant may be beneficial in selected infants with secondary respiratory failure from various etiologies (68). A recent pilot study was completed administering surfactant to premature infants who experienced a secondary respiratory failure after recuperation from primary RDS (68). The findings from this study suggest that secondary surfactant dosing may be effective in reducing oxygen and ventilatory requirements in this group of neonates.

With injury to the lung there may be contamination of the surfactant and/or disruption of type II cell activity leading to decreased amounts of available DPPC and proteins with a subsequent decrease in surface activity. As research continues, one type of surfactant may prove to be more desirable than another for treating a specific disease process, thus leading to better outcomes. Current trials with surfactant include comparing the different surfactants, timing of surfactant and delivery of surfactant. Studies are also examining other uses for surfactant in relationship to nitric oxide, congenital diaphragmatic hernia, cystic fibrosis, asthma and liquid ventilation.

Conclusion

Understanding surfactant composition, metabolism and function is essential for all health care providers. Surfactant replacement therapy has proven to be critical in caring for premature infants with RDS. Newer research indicates there may be a role for surfactant therapy in the treatment of secondary respiratory diseases in the neonatal, pediatric and adult populations. Understanding surfactant function and composition may be the key to choosing the best product for different respiratory diseases in the future.

The ability to administer the hydrophilic proteins, SP-A and SP-D, may change the way we currently treat respiratory diseases. The development of the newer synthetic surfactants with surfactant like proteins or the addition of proteins to natural surfactants holds much promise for improved outcomes.

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MANUSCRIPT TWO

SECONDARY SURFACTANT DYSFUNCTION AND DEFICIENCY

Introduction

More than 500,000 infants are born prematurely each year and most will have respiratory distress syndrome (RDS) at birth[6]. After recovery, premature infants can have a secondary respiratory decompensation that results in acute deterioration reflected by necessary increases in oxygen and ventilator support[1]. The requirements for respiratory support often continue for weeks[2, 3]. In 30% of low birth weight infants, lung disease will progress to bronchopulmonary dysplasia (BPD), defined as a continuing requirement for supplemental oxygen and /or positive pressure ventilatory support at 36 weeks postmenstrual age[4, 5]. This progressive respiratory failure is probably multifactorial secondary to oxygen toxicity, volutrauma associated with mechanical ventilation, infection, patent ductus arteriosus (PDA), and inflammation, resulting in arrest of alveolar development and interstitial fibrosis[4]. In some infants, this respiratory decompensation can lead to respiratory failure and subsequent death.

Secondary episodes of respiratory failure often lead to acute lung injury and damage to the surfactant system carrying significant risk for the preterm infant struggling to develop respiratory competence. Merrill et al. analyzed 248 tracheal samples in 68 infants who remained ventilated after 7 days of life[24]. They found that 75% of infants < 30 weeks gestation who remained intubated had dysfunctional surfactant associated with both infection and respiratory deterioration measured by their respiratory severity score

(RSS). Alterations in surfactant function caused by alveolar capillary damage, alterations in Type II pneumocytes and inflammatory cell activation lead to problems with lung mechanics and gas exchange. Surfactant replacement distributes a more uniform tidal volume among the alveoli and might reduce the damage caused by mechanical ventilation while helping to decrease atelectasis, improve lung compliance and decrease pulmonary shunting.

Surfactant therapy has been proven effective in the management of infants with initial RDS, but little research has been done on secondary events that can lead to surfactant dysfunction or deficiency (SDD) in these premature infants. Surfactant dysfunction and deficiency may accompany other diseases such as meconium aspiration syndrome, pulmonary hemorrhage, neonatal pneumonia, sepsis, and persistent pulmonary hypertension of the newborn and studies looking at surfactant replacement in these diseases have shown clinical improvement[22, 72, 73, 78, 82-84, 86-88, 92, 105-117]. There are only a few small studies looking at secondary SDD in premature infants who have recovered from RDS. These studies have looked at the effects of secondary surfactant for infants who have diffuse haziness on chest x-rays or remained ventilated after a week of age[97, 98, 118, 119]. A recent study by Katz and Klein (2006) evaluated repeated surfactant dosing in a retrospective cohort of extremely low birth weight infants over a three year time frame [98]. They identified 25 patients with post-surfactant slump after 6 days of life, who received secondary surfactant dosing after treatment for RDS. A significant improvement in both lung disease and respiratory severity was documented in 70% of these patients. All of these studies solidify the need for further research to

evaluate the efficacy and safety of administering surfactant to infants with secondary SDD.

Previous studies, as well as our own case series, report that exogenous surfactant my be beneficial in selected infants with secondary respiratory decompensation from various etiologies [84, 97, 98, 108, 109, 113, 117-119]. This preliminary evidence suggests that exogenous surfactant may be useful in treating secondary respiratory disorders that occur after recovery from RDS and may expedite recovery, diminish morbidity and lower the cost of care. The objective of this study was to look at the effect of secondary surfactant on a population of premature infants with respiratory decompensation after recovery from RDS. Secondary surfactant administration may improve functional residual capacity, compliance and decrease intrapulmonary shunting as evidenced by improvement in ventilation, oxygenation and pulmonary function. The study was designed to look at changes in respiratory severity by analyzing oxygenation, ventilation and effects on pulmonary function.

Methodology

This prospective, non-randomized, un-blinded, pilot study, in which infants acted as their own control, was designed to evaluate the short term efficacy of surfactant administration to neonates who experience respiratory decompensation similar to adult respiratory distress syndrome (ARDS) after recuperation from primary RDS.

Eligibility and Entry Criteria

Infants were eligible for the study if they were $\geq$ 7 days but $\leq$ 3 months of life, with birth weights > 500 grams and an admitting diagnosis of RDS. Prospective informed consent was obtained from the parents to enable rapid administration of surfactant at the time of respiratory decompensation.. Infants qualified for the study if

they met the eligibility criteria and then demonstrated an acute pulmonary decompensation that was non-cardiac in origin, accompanied by bilateral, diffuse parenchymal lung disease on chest x-ray and required an increased amount of respiratory support as defined as:

- Infant on a nasal cannula, hood oxygen or nasal continuous positive airway pressure (CPAP) who required re-intubation and mechanical ventilation due to respiratory deterioration; or
- Infant on minimal ventilator settings who required increased ventilatory support defined as an increase in both mean airway pressure (MAP) ≥ 2 above the infant's baseline, and in absolute FiO_2 by 20% or more above baseline and sustained for 4 hours; or
- Infant who required high frequency ventilation at the time of the respiratory decompensation.

Infants were excluded for the following reasons: congenital heart disease or lethal congenital anomalies, untreated PDA by cardiac echo or with clinical evidence of a PDA, untreated pulmonary air leak, hematocrit less than 30 %, or participation in other respiratory clinical trials. Patients with a hematocrit less than 30 % were first transfused and stabilized before being entered into the trial.

Surfactant and Study Protocol

In this pilot study, three different surfactants, Survanta, Infasurf and Curosurf, were used because they contained different amounts of surfactant proteins and phospholipids. Due to subsequent problems obtaining Infasurf in our institution, only one patient received Infasurf (I) at the beginning of the study. All other patients received

either Survanta (S) or Curosurf(C). Patients were given S or C on an alternating basis (quasi-randomization).

Infants received 4cc/kg of Survanta, 3cc/kg of Infasurf or 2.5 cc/kg of Curosurf (1.25cc/kg on second dose) per manufacturer recommendations for the treatment of RDS. A standardized method for administering the surfactant based on Neonatal Intensive Care Unit (NICU) protocol was utilized throughout the study. Infants were manually bagged for surfactant administration, and all adverse events were documented.

Infants were eligible to receive 2 doses during the 24-hour study period. The first dose was administered within 4 hours of qualification, and the second dose was 12 hours after the first dose. Patients who remained intubated 12 hours after the first administration and whose MAP was > 7 and FiO_2 > .40 qualified for the second administration. Infants were placed back on the ventilator immediately after surfactant administration, and ventilator settings were adjusted to meet the following blood gas goals: pCO_2 of 45-65, as required to keep the pH > 7.25 after treating metabolic acidosis and oxygen saturations of 92-96%, in accordance with NICU standards at our institution. If excessive chest rise or tidal volumes were noted after surfactant administration, settings were adjusted immediately.

Adverse events of desaturations, bradycardia, and endotracheal tube occlusion associated with each surfactant administration were recorded on a case report form and an adverse event log. Desaturations, as adverse events, were documented whenever oxygen saturations were less than 10 points below baseline for > 2 minutes, despite manual ventilation with 100% oxygen. Bradycardia was defined as a drop in heart rate of >20% below baseline, lasting more than two minutes despite manual ventilation. Serious

adverse events that occurred within 4 hours of surfactant administration were also recorded. Serious adverse events were defined as: Grade III or IV intraventricular hemorrhage; significant bronchospasm requiring treatment with a bronchodilator; Radiographic or other evidence of air leak, PIE or pulmonary hemorrhage; and sustained changes in heart rate or blood pressure of > 20%.

Outcome Assessment

The primary outcome was a change in respiratory status at 12 and 24 hours following secondary surfactant therapy. Changes in oxygenation and ventilation were measured by partial pressure of oxygen (PaO_2), partial pressure of carbon dioxide (PCO_2), pH, MAP, FiO_2, intermittent mandatory ventilation (IMV), and Delta P (ΔP). Secondary data analysis was performed to look at respiratory severity in response to surfactant administration. This secondary analysis was performed to insure that changes in the PaO_2, PCO_2, pH, and FiO_2 were related to improvement due to surfactant dosing and not changes in the ventilator settings. Changes in pulmonary function were measured by analyzing changes over time with the ventilatory efficiency index (VEI), modified ventilatory index (MVI) and the respiratory severity score (RSS). These measurements were documented prior to surfactant administration and at 12 and 24 hours post-administration.

The VEI was used to allow for a direct comparison of PCO_2 with changes in the ventilator. The VEI is defined as alveolar ventilation divided by the difference in ΔP (PIP – PEEP), multiplied by the frequency of the ventilator. Alveolar ventilation is the ratio of carbon dioxide (CO_2) production to the mole fraction of alveolar PCO_2 [120]. This index allows comparison of respiratory status when both ventilator pressures and PCO_2 values vary [118, 120]. Since VEI will increase as pulmonary function improves,

it allows for a measurement of changing lung function over time. Infants on High Frequency Ventilation (HFV) were excluded from VEI analysis since research has not been done using this analysis in these situations.

The MVI allows for analysis of the PIP, PCO_2, and rate and gives an indication of oxygenation and improvement in lung function. It has been used in congenital diaphragmatic hernia (CDH) research to predict prognosis [49, 121] and one study was able to show that MVI was more predictive of outcome than PCO_2 alone [51]. Since high MVI scores have been related to lung injury secondary to mechanical ventilation, a response to surfactant would be indicated by a reduction in MVI. To calculate MVI multiply PCO_2 X PIP X ventilator rate and divide by 1000 [47, 48, 117].

A respiratory severity score has recently been used to measure the severity of each patient's lung disease and response to surfactant therapy. The RSS is a modification of oxygen index without the need for PaO_2 values, allowing for a simple measure of severity of lung disease in intubated patients with the same oxygen saturation goals[24, 98]. It is calculated as the Fraction of inspired oxygen (FiO_2) x MAP. Increases in oxygenation are directly related to increases in MAP and in infants with respiratory decompensation with poor lung compliance, a higher MAP is often required. A positive response to surfactant would be indicated by a reduction in RSS through improvement in MAP and FiO_2.

Whenever possible, Arterial Blood Gases (ABGs) were obtained for analysis; however, indwelling arterial lines are not always available in this population of infants. An arterial puncture was attempted twice in any infant without an arterial line. If an ABG was not obtained at this time, a venous or capillary blood gas (VBG/CBG) was

accepted for analysis. Blood gases were obtained within 1 hour of surfactant administration, and then after surfactant administration at 1-2 hours, 12 hours and 24 hours (12 hours after the second administration).

X-rays were also reviewed by pediatric radiologists blinded to the study, pre-administration and 24 hours post-administration to look for improvement.

Statistical Analysis

To analyze changes over time, analysis of variance (ANOVA) for repeated measures was utilized. Post hoc analysis utilizing paired t-tests were performed when the ANOVA was significant. Significance levels were set to alpha = 0.05. For the purposes of statistical analysis, patients were compared over 3 time periods: Pre-surfactant; 12 hours after dose 1 but before dose 2; and 12 hours after dose 2 (corresponding with 24 hours after dose 1). Results were analyzed using SPSS (SPSS Inc., Chicago, IL, USA).

This study was approved by the Human Investigations Review Board at the Medical University of South Carolina (MUSC).

Results

Demographic Data

The Neonatal services at MUSC admit an average of 940 preterm infants (23-37 weeks gestation) each year. Approximately 37% (348) will be admitted with a diagnosis of RDS and of these 77% will be treated with surfactant. Between January 2001 and November 2002, 51 infants were consented for the study. All of these infants had received Survanta for primary RDS at birth. Twenty of these infants had qualifying events related to blood stream infections or pneumonia and received secondary surfactant treatment. Nine infants received Survanta (S), 10 infants received Curosurf (C) and 1 infant received Infasurf (I). Seventeen of the infants entered into the study between 7 and 30 days of age. Three infants developed respiratory failure later in their hospital course

and entered the study at 32, 45 and 77 days. Table 1 lists important characteristics of the 20 infants.

Characteristic	Mean (Std Deviation)	Range
Maternal Age	28 (6.5)	18-41
Gestation Age (Weeks)	25 (1.2)	24-29
Birth Weight (Grams)	813 (163.8)	520-1200
Apgar at 1 minute	4 (2)	1-9
Apgar at 5 minutes	6 (2)	1-9
Number of doses of surfactant at birth	3 (1)	1-4
Age in days at entry into study	20 (16.6)	7-77

Table 1: Maternal and Infant Demographics (n=20)

Sixteen (80%) of the 20 mothers received prenatal care, and four were unknown. Twelve (60%) had no maternal illness, 4 (20%) were diagnosed with chorioamnionitis, and 4 (20%) with hypertension. Preterm labor was present in 16 (80%) of the mothers. Only 1 patient was exposed to ruptured membranes for fewer than 18 hours; 16 patients (80%) were exposed between 18 and 24 hours. Maternal steroids were given to 18 (90%) of the mothers, with 1 not receiving steroids and 1 unknown. Sixteen infants (80%) were inborn, with 4 (20%) being transported in from another hospital. Seven infants (35%) were born by vaginal delivery and 13 (65%) by cesarean section.

Primary Outcome Variables: Oxygenation and Ventilation

One way ANOVA of secondary surfactant effects on dependent variables within subjects before initial surfactant administration and at 12 and 24 hours was performed. A significant difference was found in PCO_2 ($p<0.001$), pH ($p<0.001$), MAP ($p<0.05$), and

FiO_2 ($p<0.05$) at both 12 and 24 hours after surfactant administration. There was no significant difference in IMV or ΔP.

Paired T-tests were preformed to identify the difference between groups after the ANOVA indicated a significant difference existed. The results of this analysis indicated a significant improvement for PCO_2, pH, MAP, and FiO_2, when comparing values prior to dosing and after secondary surfactant administration at both 12 and 24 hours. This improvement was maintained in all patients for at least 24 hours after the first surfactant administration. The response to surfactant therapy for both PCO_2 and pH are reflected in Figures 1 and 2. Similar results were found with both MAP and FiO_2. These values represented means for all 20 infants during 3 periods of time, showing improvement in their respiratory status following secondary surfactant administration. No patients deteriorated during this time.

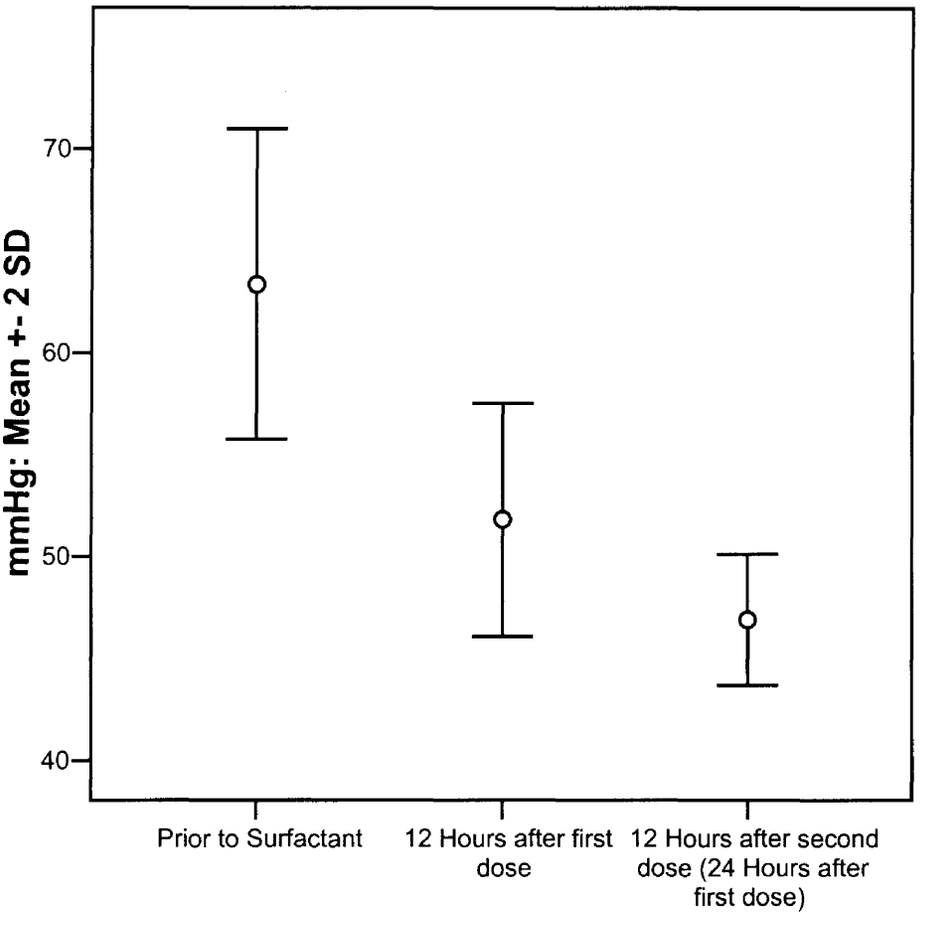

Figure 1: Mean change in PCO_2 over time.

Figure 1 displays the change over time of PCO_2. There was a significant decrease in PCO_2 from a mean of 63 mm Hg prior to surfactant dosing to 52 mm Hg 12 hours after the dose (21%, p =0.006) and 47 mm Hg 24 hours after the first dose correlating with 12 hours after the second dose (34%, p=0.001). This improvement in PCO_2 was found even when controlling for ventilatory changes.

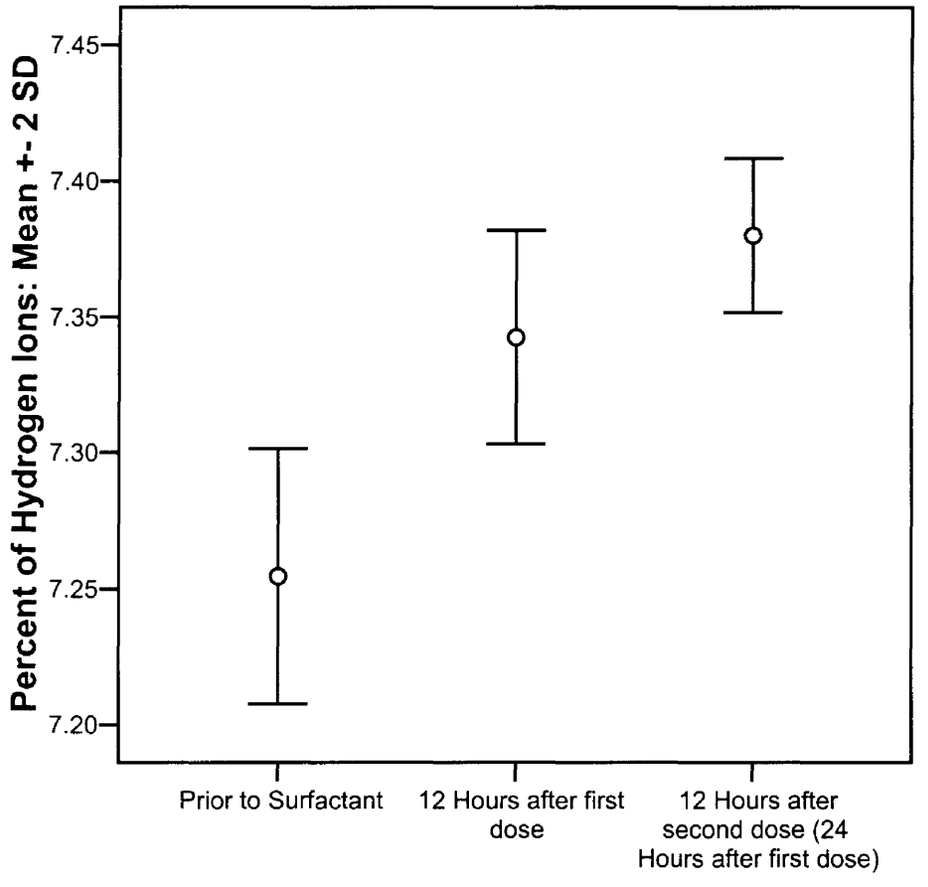

Figure 2: Mean change in pH over time

Figure 2 displays the change over time of pH. There is a significant increase over time from pre-surfactant to 12 hours ($p=0.005$), and this increase was sustained at 24 hours ($p=0.001$). None of the infants received bicarbonate treatment during the time of secondary administration. The overall pH was increased by 2% (0.13) from pre-surfactant to post-surfactant administration.

We observed improvement in MAP and FiO_2 ($p<0.05$) over the same time period. There was a significant decrease of 7% (0.6 cm of water) in MAP over time from pre-surfactant to 12 hours post surfactant ($p=0.02$), and this decrease was sustained at 24 hours ($p=0.004$). There is a significant decrease in FiO_2 over time from pre-surfactant to 12 hours post surfactant ($p=0.028$), and this decrease was sustained at 24 hours ($p=0.031$). The mean overall drop in FiO_2 was 10 mmHg (15%) from pre-surfactant to post-surfactant administration.

Secondary Data Analysis: Pulmonary Function

The ANOVA showed a significant difference in MVI ($p<0.004$) and RSS ($p<0.001$) at both 12 and 24 hours after surfactant administration. There was no significant difference in VEI. Paired t-test results for both MVI and RSS were significant when comparing scores prior to dosing and at 12 ($p<0.005$) and 24 hours ($p<0.004$) after the first dose. There was no significant difference when comparing changes from 12 to 24 hours; however the improvement was sustained during this time frame. MVI scores decreased significantly indicating improvement in pulmonary function reflected by improvement in PCO_2, PIP and ventilator rate. RSS scores also decreased significantly indicating an improvement in the severity of respiratory disease (Figure 3). Seventy-five percent of the infants had a significant improvement in their RSS and in 50% of these, there was greater than fifteen percent improvement in RSS.

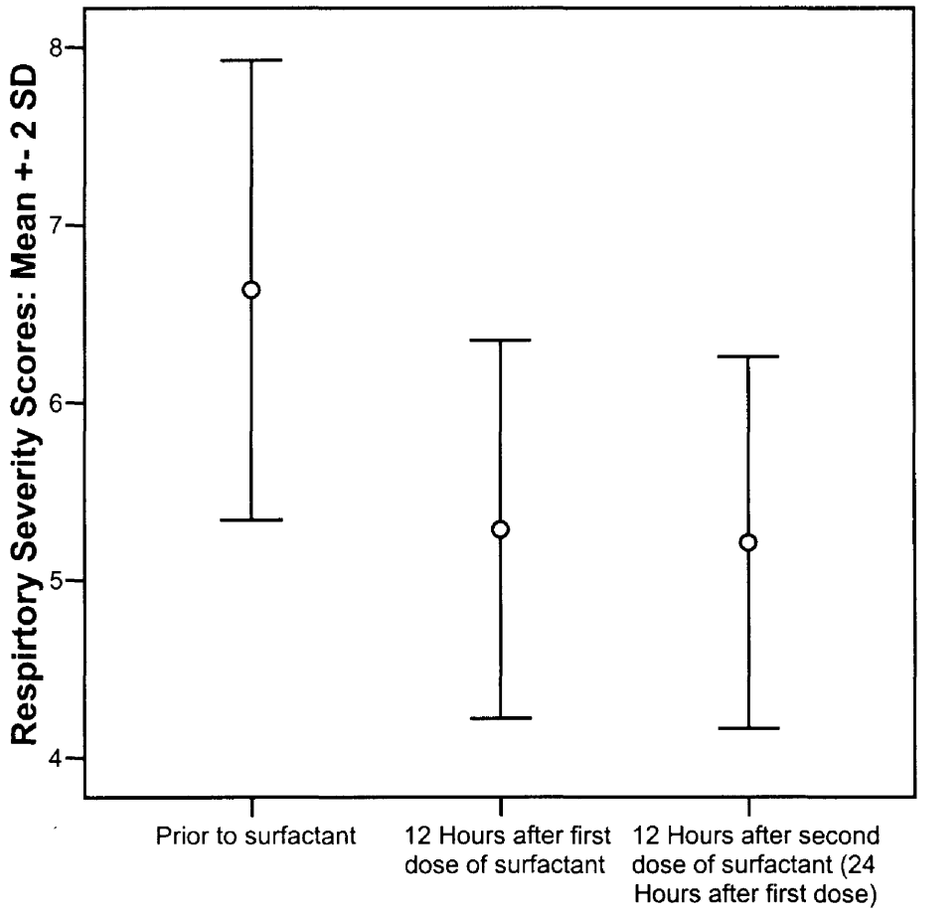

Figure 3: Mean change in RSS over time

Figure 3: Respiratory severity scores (RSS) in infants (n=20) treated with surfactant after respiratory decompensation. There was a significant reduction in the mean RSS prior to surfactant dosing and at 12 and 24 hours ($p<0.001$). There was no significant improvement in RSS from 12 to 24 hours.

Surfactant

Secondary analysis compared S and C groups to changes in ventilatory responses prior to surfactant dosing and at 1-2, 12 and 24 hours after dosing. No differences were found between the two groups when comparing FiO_2, MAP, ΔP, IMV, VEI, MVI or RSS 1-2 hours after dosing. However, a significant difference was noted between the two groups 1-2 hours after surfactant administration for PCO_2 and pH. Figure 4 compares the two groups of infants and displays changes over time for PCO_2. There was a significant decrease in PCO_2 ($p<.005$) and a significant increase in pH ($p=.006$) 1-2 hours after surfactant administration in the Curosurf group compared with the Survanta group. There was no significant difference between S and C groups at 12 or 24 hours.

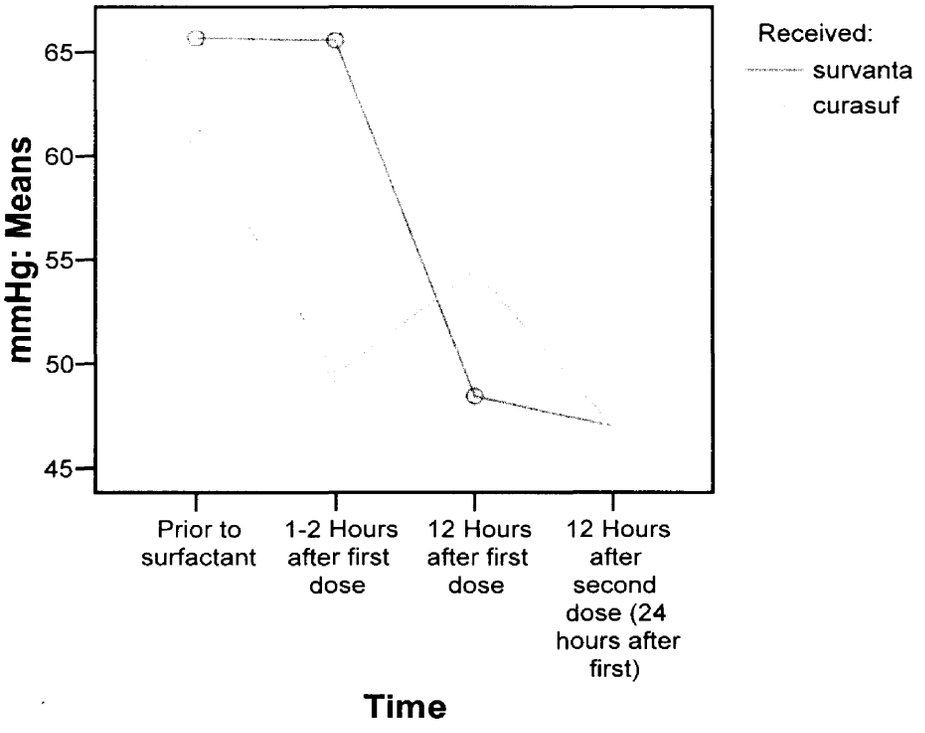

Figure 4: Comparison of type of surfactant and change in PCO_2. There was a significance decrease in PCO_2 at 1-2 hours after surfactant dosing ($p < 0.005$) with a more rapid change noted in the Curosurf group. This difference between surfactants was not sustained and there was no difference between the two surfactants at 12 or 24 hours post dosing.

Chest radiographs were read by pediatric radiologists in a blinded fashion before the first surfactant administration and 24 hours later. Diffuse parenchymal lung disease was confirmed in all cases for infants admitted to the study. Nineteen infants had follow-up x-rays 24 hours after surfactant administration. Fifty percent of these x-rays showed an overall improvement in aeration, 25% were unchanged, and 20% had increased opacities.

Adverse Events

There were 6 adverse events reported during the study dosing. Four infants (20%) had an episode of desaturation to 80% lasting approximately 2 minutes, after the first dose and 2 infants (10%) had desaturations of the same magnitude after the second dose. One of these infants with an occluded endotracheal tube after the surfactant dosing,

responded to an increase in PIP for 5 minutes. The serious adverse events documented during the study included 2 infants who had unstable saturations before dosing, with desaturations to 50-60% with dosing (1S, 1C). Of infants receiving secondary surfactant dosing, 3 infants died, two from necrotizing enterocolitis (1C, 1I) and 1 from overwhelming pseudomonas sepsis (S). Although these infants died 10 days, 12 days and 192 days after the study this outcome data was reported as a serious adverse event. Other serious adverse events such as IVH, bronchospasm, or air leak were not observed. .

Discussion

In this pilot trial, analysis of oxygenation and ventilation demonstrated an improvement when compared pre- and post surfactant administration. There was a significant improvement in oxygenation with an ability to wean MAP and FiO_2, consistent with previous studies evaluating prophylactic surfactant in the treatment of RDS [41, 42]. There was improvement in both pH and PCO_2 without significant changes in IMV, or ΔP during the 24 hours after surfactant administration, suggesting that the improvement may have been due to the surfactant dosing.

Analysis of pulmonary function demonstrated an improvement in MVI and RSS at 12 and 24 hours. Accurate measures of the severity of respiratory disease are important both clinically and epidemiologically with significant improvements in MVI and RSS indicating improvement in pulmonary function and lung disease. Discrepancy between the intensity of mechanical ventilation and the severity of respiratory disease can have serious consequences. Blood gases can be misleading, when impaired gas exchange, with increased PCO_2 levels, are due to inappropriate ventilator settings, leading to inadvertent positive end expiratory pressure (PEEP) or obstruction of the pulmonary circulation. Even in severe lung disease, a high PEEP would probably result in improvement in PaO_2

at any FiO_2.. Variables such as MVI measure the intensity of therapy taking into account variations in ventilator management by incorporating both therapies (ventilator rate and PIP) and response to therapy (PCO_2). Both MVI and RSS are less provider dependent than some of the others parameters measured.

This study showed that repeat surfactant therapy significantly improved oxygenation, ventilation and reduced the severity of lung disease in this group of infants. Despite these findings, 3 infants did not demonstrate an improvement in their RSS. Lack of response to secondary surfactant may be related to injury to the lung prior to the surfactant dosing, increased alveolar capillary permeability and secondary surfactant inactivation by the proteins that leaked in to the alveolar space. Structural immaturity of the lung or other pathophysiologic conditions unrelated to surfactant deficiency may also affect response to surfactant. All of the infants in this study decompensated secondary to pneumonia or sepsis. Premature infants with a respiratory decompensation from pneumonia or sepsis are at risk for SDD due to injury to Type II alveolar cells. Atelectasis, capillary leak of fluid and protein, alveolar inflammation, and the release of inflammatory mediators may cause surfactant dysfunction, leading to deficiency and contributing to the development of BPD. There have been several small studies demonstrating that infants with sepsis or pneumonia who received secondary surfactant have improvement in gas exchange [98, 108, 113, 122]. This study adds to that growing body of evidence.

When looking at the group as a whole, infants did not have improvement in ventilation and oxygenation in the first hour after surfactant administration. However, in our small sample size, a significant difference in both PCO_2 and pH was noted 1-2 hours

after surfactant administration when comparing the Survanta to Curosurf group. Infants in the Curosurf group had significant improvement in both PCO_2 and pH immediately after administration. This improvement may be related to surfactant properties or composition. Significant improvement was noted in both groups at 12 hours, and this significance was sustained at 24 hours. Future studies comparing surfactants may be important in infants with secondary respiratory failure secondary to SDD.

The administration and dosing requirements for surfactants in infants with SDD is unknown. Experimental studies have shown that response to surfactant may depend on the type of pulmonary injury and the degree of surfactant dysfunction or inhibition. [123]. Response to surfactant may also be influenced by the timing of treatment [123], the type of surfactant used [124], the way surfactant is administered [123], the volume of the dose and the number of doses[125]. The majority of surfactant studies have used bolus administration in divided doses with the total volume of surfactant standardized by patient body weight for calculating dose [109, 126-129]. Bolus administration using a dual lumen endotracheal tube or catheter has been shown to be effective and may cause fewer adverse events [130]. For treatment of respiratory decompensation other than RDS, there was no benefit seen with more than two additional doses and the benefit from a single dose appears to persist for approximately 12 hours [114, 115]. Based on these studies, we chose to administer 2 bolus doses of surfactant, consistent with recommendations for infants with RDS. Clinical deterioration and the need for increased ventilatory support seen in some infants 12 hours after administration may indicate the need for additional surfactant treatment or the doses may not be large enough for infants

with SDD. Further research is needed to determine the most effective dose, frequency and method of administration in this group of infants.

The few adverse events related to dosing were limited to desaturations and bradycardia, which were easily managed by increasing peak pressure or FiO_2 during administration. The 3 infants who later died in the study were reported as serious adverse events; however these deaths may be associated with coincidental pathology or multi-organ failure, or perceived treatment futility due to pre-existing diagnoses instead of unsupportable respiratory failure. The pilot study shows that secondary surfactant administration may be tolerated without serious adverse events.

There were several limitations to this study. It was a prospective, non-randomized pilot trial which could introduce biases into outcome measures. An unblended medical team could lead to differences in ventilator management in the study patients and there was no control group. It is important to point out that the pilot trial was designed to improve later study design and power analysis in determining outcome parameters most sensitive to treatment and adverse events associated with secondary surfactant administration.

The study also allowed for a large heterogeneous study group with different respiratory etiologies to identify types of patients who may benefit from secondary surfactant dosing. Only 4 of the infants had BPD upon entry into the study. At the time of respiratory decompensation all the infants were diagnosed with either pneumonia or confirmed sepsis. None of these infants had a diagnosed PDA on entry into the study or within a week after the study. Also none of these infants required lasix or steroids before, during or immediately after (within 3 days) of the trial. Although our results are

encouraging, larger randomized controlled trials are needed to see if secondary surfactant administration can effectively treat this vulnerable patient population.

Another limitation of the study was our inability to obtain arterial gases in each patient. The age of this infant population made obtaining arterial results difficult as most of the infant did not have arterial access at the time of decompensation. The majority of patients received an initial ABG followed by CBGs or VBGs. We, therefore, could not analyze differences in PaO_2 and had to compare pH and PCO_2 values from a pre-dosing ABG with a post-surfactant administration CBG or VBG. It was important to take into consideration that PCO_2 levels are elevated and pH levels lower in VBG or CBG samples, compared to arterial levels. Therefore if surfactant decreases PCO_2 values post-administration, then comparing lower PCO_2 in a pre-administration ABG to a post-administration VBG would tend to minimize the effect of the surfactant, and the bias would be against surfactant having an effect. This would tend to underestimate the treatment effect, but would not overestimate it. A similar bias against surfactant effect on pH would apply. This technical difficulty could be overcome by placing an arterial line, which might be considered in the design of a larger trial.

Respiratory failure in premature infants is a complex pathophysiologic process with many different causes. Although there are limitations in current research, there is a small but growing body of evidence that surfactant treatment for respiratory decompensation is promising. With increased survival of very low birth weight infants it is important to outline strategies that will improve care. Premature infants often have several episodes of respiratory decompensation during their hospital course that impact long-term outcomes, such as length of stay and incidence of BPD. . In addition, non-pulmonary pathology

leading to multi-organ failure despite the administration of surfactant, may negatively impact outcomes despite initial pulmonary improvement. Although secondary surfactant administration may improve oxygenation and ventilation on a short-term basis, it is unknown whether these improvements will be sustained long-term.

Conclusion

Although this was a small non-randomized pilot study, we found that surfactant was efficacious for improving gas exchange and decreasing ventilatory support in premature infants with presumed secondary SDD. This trial suggests that premature infants > 7 days of life, with a secondary respiratory decompensation may derive short term benefits from exogenous surfactant administration, resulting in improved oxygenation, ventilation and pulmonary function without serious adverse events. Long term benefits may involve fewer days of mechanical ventilation and shorter hospital stays. Large, prospective, randomized controlled studies are needed to understand the role of surfactant in treating infants with SDD. Researchers need to look at both short- and long-term clinical outcomes and begin to evaluate the efficacy of administering surfactant to neonates who experience respiratory failure after recuperation from their initial RDS.

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SUMMARY AND CONCLUSION

Respiratory Distress Syndrome is a developmental disorder that has an increased incidence and severity with decreasing gestation age. The clinical pattern in the first week of life usually includes episodes of respiratory decompensation necessitating an increased need for inspired oxygen and ventilatory support. Most infants will recover from RDS; however approximately 30% of these infants will go on to develop BPD or respiratory failure secondary to oxygen toxicity, volutrauma associated with mechanical ventilation, infection, PDA and inflammation. Premature infants are at increased risk for secondary SDD due to a decrease in the secretion of surfactant phospholipids in the lungs and a longer recycling time of surfactant [131]. Their surfactant also has decreased biophysical function and is more sensitive to inactivation by inhibitors due to the decreased amounts of surfactant proteins [131]. Additional studies are needed to see if there is a role for surfactant treatment in premature infants after the first week of life that have respiratory decompensation or failure requiring mechanical ventilation.

To understand secondary SDD in preterm infants it is important to not only understand the effects of diseases on the lungs but also the composition and actions of surfactants in the lung and how they are affected by these diseases. Infants who develop a secondary respiratory decompensation due to SDD often require mechanical ventilation. Mechanical ventilation leads to volutrauma and barotrauma and the increased need for oxygen causes oxygen toxicity. This causes damage to the type II pneumocytes leading to alterations in the synthesis, storage and release of surfactant which is already delayed

in premature infants. Sepsis, pneumonia, atelectasis and PDA's in these infants lead to capillary leak of fluids and proteins, pulmonary edema and alveolar inflammation. This leads to inhibition and inactivation of surfactant. Release of inflammatory mediators also leads to interference with surfactant function and processing. Infants who appear to recover from RDS but then have a slow deterioration with a continued RDS picture (post-surfactant slump) may have decreased amounts of surfactant with an increased susceptibility to inactivation. These may be especially important in the extremely premature infants whose surfactant continue to function poorly despite initial surfactant replacement for RDS. Surfactant replacement may be beneficial in all of these infants.

There are currently no large, randomized controlled trials looking at secondary SDD in premature infants who have recovered from their initial RDS but go on to develop secondary respiratory deterioration or failure. This work includes the first prospective pilot study looking at the effects of surfactant on premature infants who have recovered from RDS but who later have a respiratory decompensation consistent with SDD. The findings suggest that surfactant given to these patients may provide short term improvement in oxygenation, ventilation and pulmonary function. Secondary lung injuries where surfactant has become deficient or inactive may be treated with endogenous surfactant. Further research is needed to see if there is a decrease in the incidence of BPD, days in the hospital and mortality in these patients.

It is important to note that there are several limitations to the current work including the fact that this was a non-randomized, non-controlled, unblinded study with a small sample size. Respiratory failure is a complex, pathophysiologic process with many different causes and the long term impact of secondary surfactant administration on infant

outcomes is limited. Non-pulmonary pathology may lead to multi-organ failure despite the administration of surfactant. It is also not known which of the many surfactant properties will account for the potential benefits of surfactant administration in this group of neonates.

The uses of surfactant for other diseases in neonates that lead to SDD are being studied. Future research is needed to look at the dosage, administration and timing of surfactant for infants with SDD. These infants may need larger doses than infants with RDS due to pulmonary damage. Bolus administration needs to be compared to lavage administration in this group of patients. Surfactant timing may need to be individualized for each patient based on RSS or MVI. Providing a standardized dosing pattern for infants with varying degrees of pulmonary injury may not be the best method. Exogenous surfactant composition may need further research to look at the need for additional surfactant proteins and products that reduce surfactant inhibition. These newer surfactants may be more resistant to inhibition and provide surfactant proteins A and D for host defense. The next generation of surfactants may lead to designer surfactants for individual patients and diseases. The next step will be a randomized, controlled trial analyzing surfactant protein composition and the effects of secondary surfactant dosing on oxygenation, ventilation and pulmonary function in premature infants who recover from RDS but go on to develop a secondary decompensation.

APPENDIX

IRB APPROVAL

HRRA Changes http://erma.musc.edu/irb_hrra/hrra_changes.cgi?Doc_Number=5333

HR Number : 10001
Submission date : 08/03/2001
Meeting date : 09/04/2001
Termination Date:

Study Status : Approved
Approval date : 09/04/2001
Approval expiration : 06/01/2007
Current Approval: 06/02/2006

Title: Treatment of Secondary Surfactant Deficiency in Neonates

View/Print Forms

Human Research Review Application

PI Statement of Assurance ☑
(signature page)

Attachments

Manage submission

History of changes

Change Access to the study

Report Adverse Events

Adverse Events

Report Amendments/Continuing Review

Amendments

Continuing Review (Coming soon)

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