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Surfactant Therapy for Respiratory Distress Syndrome in Premature Neonates

A Comparative Review

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Abstract

Exogenous surfactant therapy has been part of the routine care of preterm neonates with respiratory distress syndrome (RDS) since the beginning of the 1990s. Discoveries that led to its development as a therapeutic agent span the whole of the 20th century but it was not until 1980 that the first successful use of exogenous surfactant therapy in a human population was reported. Since then, randomized controlled studies demonstrated that surfactant therapy was not only well tolerated but that it significantly reduced both neonatal mortality and pulmonary air leaks; importantly, those surviving neonates were not at greater risk of subsequent neurological impairment.

Surfactants may be of animal or synthetic origin. Both types of surfactants have been extensively studied in animal models and in clinical trials to determine the optimum timing, dose size and frequency, route and method of administration. The advantages of one type of surfactant over another are discussed in relation to biophysical properties, animal studies and results of randomized trials in neonatal populations. Animal-derived exogenous surfactants are the treatment of choice at the present time with relatively few adverse effects related largely to changes in oxygenation and heart rate during surfactant administration. The optimum dose of surfactant is usually 100 mg/kg.

The use of surfactant with high frequency oscillation and continuous positive pressure modes of respiratory support presents different problems compared with its use with conventional ventilation.

The different components of surfactant have important functions that influence its effectiveness both in the primary function of the reduction of surface tension and also in secondary, but nonetheless just as important, role of lung defense. With greater understanding of the individual surfactant components, particularly the surfactant-associated proteins, development of newer synthetic surfactants has been made possible.

Despite being an effective therapy for RDS, surfactant has failed to have a significant impact on the incidence of chronic lung disease in survivors. Paradoxically the cost of care has increased as surviving neonates are more immature and consume a greater proportion of neonatal intensive care resources. Despite this, surfactant is considered a cost-effective therapy for RDS compared with other therapeutic interventions in premature infants.

Hockheim[1] is credited with the first description of the histopathological features of what was then called hyaline membrane disease but it was not until the 1950s that the nature of the hyaline membrane became clearer.[2] The discovery that surfactant deficiency was central to the pathogenesis of respiratory distress syndrome (RDS)[3] led to the first (and unsuccessful) trials investigating the efficacy of an exogenous surfactant 1,2-dipalmitoyl-*sn*-glycero-3-phosphocholine (DPPC) in the treatment of RDS.[4,5] Despite the lack of success in these early clinical trials, advances in disease treatment were made using both animal models of RDS[6] and human neonates.[7] Following this, several exogenous surfactants were developed and used in clinical trials involving patients with RDS around the world. The effectiveness of surfactant has been demonstrated in meta-analyses of randomized controlled trials (with or without the use of placebo)[8-10] and in some epidemiological studies of outcomes in low birth weight neonates.[11] The impact of exogenous surfactant in the treatment of neonatal RDS has been such that the conduct of further placebo-controlled trials are considered unethical under the Declaration of Helsinki.[12]

This review considers advances in the understanding of the structure and composition of exogenous surfactants in the treatment of RDS in the neonate, and discusses areas of debate including the type of surfactant used, the magnitude and number of doses, method of administration, the timing of the initial dose and the relationship to differing strategies of respiratory support.

1. Endogenous Surfactant Composition and Function

A common evolutionary pathway can be seen in the composition of surfactant in the lungs of air-breathing fish,[13] reptiles[14] and mammals;[15] all are phospholipid-based, but the constituent phospholipids differ. Human pulmonary surfactant is approximately 90% phospholipid and 10% protein.[16] The nature of the phospholipid in mature human pulmonary surfactant is shown in figure 1.

1.1 Surfactant Phospholipids

Although much attention is focused on the protein component of pulmonary surfactants, it is the phospholipids that form a greater part of surfactant and impart the surface tension reducing properties. Phospholipid mixtures, with or without additional spreading agents that do not contain surfactant proteins, have been shown to be effective in both *in vitro*[17] and clinical settings.[18,19]

Phosphatidylcholine (PC) is the most abundant phospholipid in surfactant[20] and is predominantly saturated with one or two palmitic acid chains. The disaturated form, DPPC, is the primary surface-active component;[21] however, pure DPPC does not adsorb rapidly to the air-tissue interface at physiological temperatures[22] nor does it spread well.[23] Other phospholipids and surfactant proteins impart these properties.[24]

1.2 Surfactant-Associated Proteins

About 10% by weight of surfactant is made up of proteins of which the most important are the four surfactant-associated proteins. Surfactant protein (SP)-B and SP-C are hydrophobic (lipid soluble) and play a major role in the surface tension lowering capability of surfactant. SP-A and SP-D are hydrophilic (water soluble) and are primarily involved in host defense and surfactant homeostasis. Of the surfactant-associated proteins, only SP-C is

specific to the lungs while the other surfactant-associated proteins can be found in surfactant-like material in the gastric mucosa.[25]

1.2.1 Surfactant Protein A

SP-A, discovered in 1972, has little effect on surface activity but instead plays an important role in surfactant metabolism, tubular myelin formation and lung protection.[26] It increases the adsorption of surfactant lipids *in vitro* in conjunction with SP-B and SP-C to maintain and enhance the lipid monolayer at the air–liquid interface. SP-A interacts with isolated alveolar type II pneumocytes, inhibiting lipid secretion and increasing lipid association within these cells.[27] However, transgenic mice that are null (–/–) for SP-A genes and that lack SP-A mRNA and SP-A protein have normal levels of phospholipid and normal lung function, although tubular myelin is absent.[28]

SP-A protects against the inhibitory effects of plasma proteins on surfactant activity *in vivo*.[29,30] Deficiency of SP-A mRNA was demonstrated in a baboon model of bronchopulmonary dysplasia[31] and low SP-A/saturated PC ratios in endogenous surfactant during the first week in very low birth weight infants are associated with greater mortality and morbidity.[32]

SP-A is related to the collagenous lectins (collectins). The latter are a group of proteins that includes SP-D, mannose binding protein, conglutinin and collectin (CL)-43, which act as opsonins in various circumstances, and are likely to have roles in innate immunity.[33] SP-A acts as an opsonin against some bacterial and viral pathogens,[34,35] as well as potentiating the antimicrobial activity of the alveolar macrophages.[36,37] Transgenic SP-A (–/–) mice are more susceptible to infection with a variety of bacterial and viral pathogens.[28]

Each SP-A molecule comprises four distinct regions[33] and is encoded by two genes.[38,39] It is synthesized within the alveolar type II cells and secreted as a large octadecameric complex assembled from 18 polypeptide chains.[40] The product of each functional SP-A gene appears to be required for stable mature SP-A;[41] the DNA sequences for these have been denoted 6A and 1A. There are several allelic variants of the SP-A 6A (gene 1) and in population studies some of these allelic variants appear to be important in predisposing to RDS.[42]

1.2.2 Surfactant Protein B

The hydrophobic proteins SP-B and SP-C were not recognized until the late 1970s.[43] SP-B is a homodimer of approximately 18 kDa with two identical polypeptide chains linked by a disulphide bridge. Each is composed of several amphipathic α-helices with hydrophobic and hydrophilic residues on opposite faces. The SP-B proprotein, contains 22 cysteine residues, and undergoes proteolysis within the type II pneumocytes[44] to give the active dimeric form.[45]

The quaternary structure of SP-B, and its interactions within the phospholipid layer, have yet to be fully delineated but it is known to contain up to four amphipathic helices that interact with the phospholipid films.[46,47] Each SP-B monomer has 3 intra-

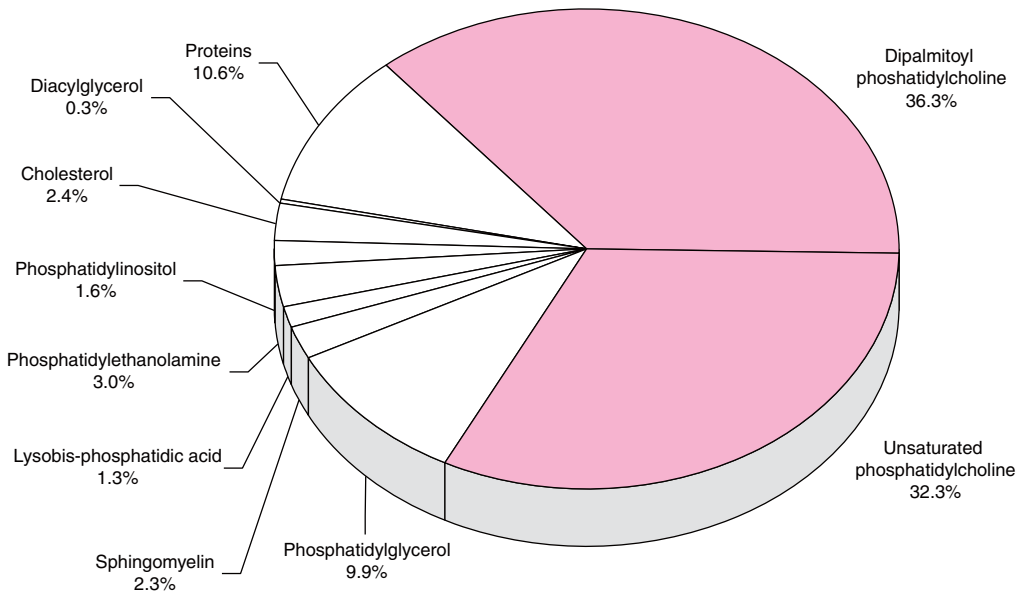

Fig. 1. Constituent components of mature human adult surfactant. The shaded area represents total phosphatidylcholine component (68.6%) [reproduced from Possmayer et al.,[16] with permission].

molecular disulphide bridges linking Cys-8-77, Cys-11-71 and Cys-35-46,[48] with a further cysteine residue at position 48 forming the intermolecular bond responsible for dimerization. Evidence from transgenic mice suggests that the Cys-35-46 disulphide bond is essential for SP-B function.[49]

SP-B is essential for surfactant function via effects on surface tension by enhancing the formation of a stable surface film.[50] Lack of SP-B results in lethal respiratory failure in both transgenic mice[51] and humans,[52] and affects the biosynthesis and catabolism of SP-C.[53]

1.2.3 Surfactant Protein C

SP-C is very hydrophobic, and is formed within the Golgi apparatus of the type II pneumocytes from a proprotein.[54] The SP-C molecule has a number of isoforms but is mainly found as a 35 residue peptide chain with a helical trans-membrane domain.[55] The size of the helix matches that of a fluid DPPC bilayer and corresponds to the trans-membranous orientation of SP-C in surfactant.[56] SP-C facilitates phospholipid film formation and enhances stability and re-spreading[50,57] by preferentially 'squeezing out' DPPC molecules at lower lung volumes,[58] it also confers some protection against inhibitory effects of plasma proteins.[59]

Transgenic SP-C (–/–) mice do not appear to have any discernible pulmonary abnormalities, although their surfactant does not function well at low lung volumes.[60] In humans SP-C gene mutations are associated with familial interstitial lung disease that may be due to recurrent atelectasis, lung injury and inflammation.[61]

1.2.4 Surfactant Protein D

SP-D is a hydrophilic collagenous glycoprotein[26] resembling SP-A in its monomeric form it but has a cross-shaped quaternary structure.[62] It does not directly affect surface tension in surfactant and most of its putative functions in the lung relate to defense against various pathogens.[29,63] It also plays a role in the homeostasis of phospholipid; transgenic SP-D (–/–) mice with no SP-D have abnormal accumulations of phospholipids.[64]

1.3 Other Proteins/Polypeptides in Surfactants

Three heptapeptides, prophenins, have been isolated from ovine surfactant.[65] These are derivatives of the cathelicidin antibacterial peptides.[66] Their synthesis and functions have yet to be delineated.[67] Similar polypeptides have been found in porcine surfactant and are preserved by the usual methods of extracting animal-derived lung surfactants.[66] These polypeptides may be responsible, in part, for some of the putative antibacterial action of exogenous surfactants.[68]

2. Exogenous Surfactants

A number of surfactant preparations have been developed independently. This section will consider those surfactants that have been reported in the medical and scientific literature considering them by their origins. Table I summarizes these surfactant preparations.

2.1 Synthetic Surfactants

Early synthetic surfactants were compositionally simple and consisted only of phospholipids with high proportions of DPPC. The earliest attempts at surfactant replacement came in the 1960s when Robillard et al.[4] and Chu et al.[5] independently investigated the effectiveness of nebulized DPPC in neonates with established RDS. Neither group reported any beneficial effects from this novel therapy and Chu et al.[5] speculated 'our findings do not agree well with the suggestion that the syndrome results from the primary lack of pulmonary surface-active material'. Since then, four protein-free synthetic surfactants have been investigated although only one, colfosceril palmitate, is still available commercially.

Pumactant [Artificial Lung Expanding Compound (ALEC®[1])] contained the phospholipids, DPPC and phosphatidylglycerol (PG) in a ratio of 7 : 3.[86,87] It was initially used as a dry powder preparation in a rabbit model of RDS[88] and neonatal populations.[89-91] However, difficulties in delivering >25mg surfactant and the finding that dissolving the surfactant in cold saline retained the surface tension reducing properties resulted in a new formulation which was then used in two further studies.[18,92]

Colfosceril palmitate (Exosurf neonatal®)[19] is composed of DPPC (84.5%), with hexadecanol (9.5%) and tyloxapol (6%) to facilitate dispersion within the lung. It is the most widely studied of all synthetic surfactants in numerous randomized controlled trials[93-107] and in comparative trials with other surfactants.[108-118]

Turfsurf or the 'Belfast surfactant', a mixture of DPPC and high density lipoproteins in a ratio of 10 : 1, was investigated by Halliday et al.[69] for its efficacy in preventing RDS, but this compound was never developed commercially.

Aposurf, reconstituted from isolated low molecular weight apoproteins, synthetic DPPC and dipalmitoyl-phosphatidylglycerol was not as effective as the natural surfactant extracts in an animal model of RDS and has not been developed commercially.[70]

1 The use of tradenames is for product identification purposes only and does not imply endorsement.

Table I. Studies with exogenous surfactant preparations reported in medical and scientific literature

Name	% DPPC	Proteins
Protein-free synthetic surfactants		
Nebulised DPPC[4,5]	100	
Pumactant (ALEC®)[18]	70	
Colfosceril palmitate (Exosurf neonatal®)[19]	84.5	
Turfsurf[69]	91	
Aposurf[70]	70	
Animal derived surfactants		
(a) Minced lung extracts		
Poractant alfa (Curosurf®)[71]	35	SP-B & SP-C
Surfactant CK[72,73]	35	SP-B & SP-C
Surfactant TA (Surfacten®)[74]	50	SP-B & SP-C
Beractant (Survanta®)[74]	50	SP-B & SP-C
(b) Lung lavage surfactant extracts		
SF-RI1 (Alveofact®)[75,76]	55	SP-B & SP-C
Calfactant (Infasurf®)[77]	53	SP-B & SP-C
CLSE (bLES)[73]	53	SP-B & SP-C
Human surfactant		
Amniotic fluid-derived[78]	36	SP-A, SP-B & SP-C (?SP-D)
Surfactants with synthetic/recombinant proteins		
Sinapultide/KL4/lucinactant (Surfaxin®)[79]	75	KL4
SP-C analogs,[80] SP-C(LEU)[81] and SP-C(LKS)[82]	70	
Recombinant SP-C proteins (rSP-C) [Venticute™][83,84]	70	rSP-C
SP-A analogs[85]	70	

ALEC® = Artificial Lung Expanding Compound; **bLES** = bovine lipid extract surfactant; **CLSE** = calf lung surfactant extract; **DPPC** = 1,2-dipalmitoyl-*sn*-glycero-3-phosphocholine; **K** = lysine; **L** = leucine; **SP** = surfactant proteins; **SP-C(LEU)** = analog of surfactant protein C with valine amino acid residues substituted with leucine; **SP-C(LKS)** = analog of surfactant protein C with valine amino acid residues substituted with leucine and lycine.

2.2 Animal-Derived ('Natural') Surfactant Extracts

Animal-derived surfactants are extracted from minced lungs or lavaged from intact lungs. A series of extraction and purification steps alter these surfactants such that they differ from endogenous surfactant. The biggest difference is that the hydrophilic surfactant proteins SP-A and SP-D are lost, but differences in the proportions of disaturated to unsaturated phosphatidylcholine are also thought to be important.[119] Surfactant proteins SP-B and SP-C are retained in the various animal-derived preparations but the quantities vary between surfactants[120,121] and within individual batches of the same surfactant.[122]

2.2.1 Animal-Derived Surfactants Extracted from Minced Lungs

The modified bovine lung surfactant used by Fujiwara et al.[7] was developed as a lyophilized powder called surfactant TA (Surfacten®). It is extracted from minced bovine lung using chloroform-methanol after a series of differential centrifugation and flotation steps before being supplemented with synthetic phospholipids.[74] It was then taken to the US where it became available more widely as beractant (Survanta®). Both versions of this minced bovine lung surfactant extract have been studied in numerous randomized controlled trials[123-131] and comparative trials with other surfactants in the treatment and prevention of RDS.[108-113,132-134]

Poractant alfa (Curosurf®) is isolated from minced porcine lungs by a process of washing, chloroform-methanol extraction and liquid gel chromatography.[71] Randomized controlled trials of poractant alfa in the treatment of RDS were undertaken in Europe.[135,136]

Surfactant CK was an extract of porcine lung and was shown to have beneficial effects on lung function when administered to preterm neonates with RDS in uncontrolled studies in the early 1980s.[72,73] It was never developed commercially.

2.2.2 Animal-Derived Surfactants Extracted from Whole Lungs

The other animal-derived surfactants are extracted from whole rather than minced lungs using chloroform-methanol and lavage techniques. SF-RI1 (Alveofact®) is a bovine surfactant extract. It was developed and tested in Europe.[75,76] Two closely related calf lung surfactant extract preparations have been developed; these are lavaged from the lungs of freshly slaughtered calves. Calfactant (Infasurf®), has been studied in centres in the US[77,137-139] whereas bovine lipid extract surfactant (bLES) has largely been studied in Canada.[140,141] A randomized trial has compared calfactant with beractant,[134] and both calfactant and bLES have been compared in randomized trials with colfosceril.[116-118]

2.3 Homologous (Human) Amniotic Fluid-Derived Surfactant

A homologous surfactant[78,142] derived from term amniotic fluid was developed using the active surfactant fraction obtained through density gradient separation and centrifugation. The final preparation contained 80 to 83% phospholipids and 5% surfactant-associated protein (including SP-A).[78] It is no longer used because of concerns about disease transmission and the difficulty in harvesting enough surfactant for widespread utilization; uncontaminated amniotic fluid from 100 births was required to make 1 gram (10 doses) of surfactant.[143]

2.4 Newer Synthetic Surfactants with Protein Analogs

Concerns that animal-derived surfactants could either transmit infectious agents or produce immune complexes[144] led to attempts to produce surfactants with synthetic surfactant proteins. Two approaches have been taken; the development of synthetic peptide analogs and use of recombinant technology. Synthetic surfactant peptide analogs, based on human SP-B and SP-C, mimic both the structural and functional properties and the *in vivo* functions of the native lung surfactant proteins[145] and offer the possibility of designing or modifying synthetic surfactant preparations.[146]

Sinapultide (lucinactant, KL4, Surfaxin®)[79] is a peptide analog which is currently undergoing clinical trials in a randomized comparison with poractant. Sinapultide consists of a 21 amino acid sequence of lysine (K) and leucine (L) that resembles the pattern of hydrophobic and hydrophilic residues found in the biologically active N-terminal part of SP-B.[147] Sinapultide is added to a 3 **:** 1 DPPC **:** PG mixture.

Other researchers have investigated a 10 residue amphipathic helix lung surfactant, similar to SP-B, which has been shown *in vivo* to improve pulmonary compliance and gaseous exchange.[148]

Takei et al.[80] investigated several peptide analogs having either the full structure of human SP-C or containing the central hydrophobic core of SP-C. These were mixed with DPPC, PG and palmitic acid. They had biophysical properties similar to beractant and, in preterm rabbits, led to improvement of ventilation and oxygenation. A recombinant 34 amino acid analog of SP-C (lusupultide, Venticute™) was shown to be as effective as the current animal-derived surfactant preparations in a rat model of RDS.[83] In the early studies this rSP-C molecule had the same amino acid sequence as human SP-C but it was later determined that the transmembrane α-helix was more important than exact duplication of the amino acid sequence.[149] Further versions of rSP-C[84] and SP-C analogs have since had substitution of several amino acids in order to mimic the α-helix of natural SP-C. The SP-C(Leu) analog was produced by substituting the valine residues in SP-C with leucine but this was found to self-polymerize.[81] Replacement of three of the leucine (L) residues with lysine (K) avoided this problem but maintained the surface activity of the SP-C molecule in phospholipid mixture.[82]

Despite the structural complexity of the natural SP-A molecule, a functional synthetic segment of 31 amino acids has been shown to further increase lung compliance in preterm rabbits when added to synthetic SP-B and SP-C than if these surfactants were used alone.[85]

3. Clinical Application of Exogenous Surfactant in Respiratory Distress Syndrome (RDS)

The earliest clinical trials of surfactant demonstrated reductions in inspired oxygen concentrations and ventilator settings compared with controls; [93,125,129] results of larger multicenter randomized controlled trials demonstrated reductions in the mortality rates of infants with or at risk of RDS. Even then there were variations in outcomes according to the patient population studied. Nonetheless, meta-analyses of these trials, dividing them into synthetic[8,9] and 'natural' (animal-derived)[10] surfactants, showed that surfactant significantly reduced neonatal and pre-discharge mortality compared with controls by about 40% and reduced air leaks by about 60% but there was no consistent effect on other complications of prematurity.

Chronic lung disease (CLD) or bronchopulmonary dysplasia (BPD) has remained one of the main long-term complications in survivors of preterm delivery. The disease originally described in 1967 by Northway et al.,[150] occurred after prolonged mechanical ventilation using high inspiratory pressures and high inspired oxygen concentrations. These neonates were more mature than those treated for RDS today, had not received antenatal corticosteroids or surfactant and lung damage was attributed mainly to barotrauma and oxygen toxicity. Unfortunately the expectation that exogenous surfactant would be a panacea was not fulfilled; there was no reduction in the incidence of CLD among surviving infants and in some studies there was an increase.[95,128]

There are several explanations for the lack of effect of surfactant on CLD. Firstly, antenatal corticosteroids and exogenous surfactant have increased the survival rates of the smallest and most immature infants who are at highest risk of CLD.[151,152] Secondly, there has been a change in the pathogenesis and presentation of CLD; many of the neonates who today develop CLD have only mild RDS[153] and do not receive aggressive mechanical ventilation. The focus of the pathological picture has shifted from the airway to the interstitium, often with apparent development arrest, sepsis (possibly even antenatal) and the presence of a patent ductus.[154]

Exogenous surfactants have been shown to be well tolerated in clinical practice. Adverse effects have been relatively few and relate largely to changes in oxygenation and heart rate during administration, and rarely obstruction of the endotracheal tube.[129,155] Transient changes in arterial blood pressure,[156] cerebral blood flow and oxygenation,[157] and depression of electroencephalogram activity have also been reported.[158] Specific immunological responses to the animal surfactant proteins present in animal-derived surfactants could not be detected during the neonatal period[159] or at 6 and 12 months of age.[160]

3.1 Which Surfactant Preparation?

Biophysical comparisons of animal-derived and protein-free synthetic surfactants have shown that the former spread faster and reduce surface tension to a greater degree.[17,161] However, *in vitro* biophysical properties do not necessarily correlate with clinical efficacy. Dry powder pumactant reduced surface tensions more effectively than pumactant liquid stored according to the manufacturer's recommendations at 4ºC,[17] yet it was less effective *in vivo*,[90] and Tween 20, a synthetic detergent, barely reduced surface tension *in vitro* yet improved lung function in a sheep model of RDS.[162]

In animal models of RDS, preparations that either contained natural surfactant proteins or one of the synthetic analogs showed greater improvements in oxygenation and lung compliance than the protein-free surfactants.[163-166] Surfactants with surfactant proteins or their synthetic analogs are also inactivated by plasma proteins and meconium to a lesser degree compared with protein-free surfactants.[120]

Animal-derived surfactants appear to be superior to protein-free synthetic surfactants in terms of their biophysical properties and their efficacy in animal models of RDS; however, differences in a clinical setting, particularly longer term, were less apparent.[108-118,167,168] These comparative studies between synthetic and animal-derived surfactants have all shown short-term improvements in ventilation and oxygenation in neonates treated with the animal-derived surfactants, but only one study[167] demonstrated a difference in mortality between the two surfactants pumactant and poractant alfa. One reason for this lack of clear difference, yet to be demonstrated in neonates, may be the presence of some endogenous surfactant; protein-free surfactant (colfosceril palmitate) instilled into the lungs of preterm lambs mixes with the endogenous surfactant present and the resulting mixture had better surface tension reducing properties in newborn rabbits than the original surfactant.[169] Whatever the reason, it is clear that the differences observed between animal-derived and synthetic surfactants in the *in vitro* studies and animal models of RDS do not translate to the human neonatal population, and population demographics such as gender and race may be more important in determining outcome from RDS than the type of surfactant used.[170]

The small (but perhaps clinically important) differences in outcomes between two surfactants may not be demonstrated with limited sample sizes of an individual trial but a meta-analysis of 11 trials using protein-free synthetic and animal-derived surfactants[171] have shown significantly fewer deaths and pulmonary air leaks in infants receiving animal-derived surfactants. There were no differences between treatment groups in the rates of chronic lung disease at 28 days of postnatal age and at 36 weeks corrected gestational age, and worryingly, there was a marginal increase in intraventricular hemorrhage (all grades) in neonates receiving animal-derived surfactants, a finding that has not been satisfactorily explained. Based on this evidence, animal-derived exogenous surfactants are the current treatment of choice although results of clinical trials comparing them to the newer synthetic surfactants with protein analogs have not yet been reported.

Studies between different animal-derived surfactants are limited. Randomized comparisons have been undertaken between beractant and SF-RI1,[132] beractant and poractant alfa[133,172] and between beractant and calfactant.[134] Comparisons have also been made between non-randomized cohorts receiving beractant and calfactant[173] and between beractant and SF-RI1.[174] Within the individual studies there appears to be little difference in long-term outcomes. However, the poractant versus beractant studies[132,172] suggest neonates treated with 200 mg/kg of poractant have a lower mortality rate than neonates receiving 100 mg/kg of beractant. *In vitro* studies suggest that minced animal lung surfactants are more susceptible to inactivation by serum proteins and this would seem to be related to the SP-B content.[120] Supplementing exogenous surfactants with recombinant hydrophobic surfactant proteins or synthetic analogs may improve their resistance.[175]

3.2 When Should the First Dose of Surfactant Be Administered?

Prophylactic administration of surfactant offers the theoretical advantage of preventing the onset of respiratory insufficiency and protein leak in many infants at risk of RDS whereas treatment of infants with only established RDS ('rescue' strategy) offers the advantage of treating only infants with clinical disease, eliminating the potential risks and costs of treating infants who are not surfactant deficient. Not all 'at risk' neonates develop RDS that is severe enough to warrant surfactant therapy; between 31.9%[176] and 63.2%[177] of neonates in the 'rescue' arms of trials comparing these different strategies did not receive surfactant.

Most protein leak occurs early in the course of RDS[178] and can be seen even in unventilated areas of the lung.[179] Exogenous surfactant reduces protein leak[178,180,181] and the earlier the surfactant is administered the more effective it is.[181-183] Manual ventilation during resuscitation can lead to changes that affect surfactant function[184] and surfactant may be distributed more homogeneously in lungs still filled with fluid,[185] raising the challenging question of whether it should be administered before the first breath.

Several studies have looked at outcomes in neonates using different strategies[106,107,186-194] but the definition of the term 'prophylaxis' remains inconsistent. The current Cochrane meta-analysis[185] and two other meta-analyses[195,196] defined 'prophylaxis' as surfactant administration in the delivery room; later administration is taken to be 'rescue' treatment. There have been a variety of criteria used to initiate 'rescue' treatment and what constitutes early or late 'rescue'.

Irrespective of the definitions used in the trials, outcome data support the use of earlier rather than later surfactant administration. Early use decreased the incidence of pulmonary air leaks and mortality, although some of the improved outcomes were only apparent in the more immature infants.[188] Unlike in animal models where surfactant administration before the first breath was more effective[181] in humans, the administration of surfactant before the first breath was no more effective than within 10 minutes of birth.[197] One explanation why this might be so is that lung recruitment maneuvers might play a role in surfactant efficacy[198,199] although there is some debate about this. Other investigators have shown no improvement in surfactant function after lung recruitment maneuvers particularly when these involve tidal volumes in excess of 10 ml/kg.[200]

There remains, however, a wide variation in clinical practice in neonatal units. Many centers routinely intubate the less mature neonates to administer surfactant and mature neonates are given surfactant only if they develop RDS and require ventilation. This approach could be further refined using surfactant maturity such as the lecithin/sphingomyelin ratio,[201] the stable microbubble test[202] or the click test.[203]

3.3 Optimum Dose of Surfactant

In clinical trials, doses of phospholipid in exogenous surfactants varied from 25mg irrespective of birth weight[89] to 200 mg/kg.[71] These doses initially had little scientific basis, although it later became evident that term neonates have a surfactant pool size of approximately 100 mg/kg[204] and neonates with RDS have a surfactant pool size of only 5 to 10 mg/kg.[205] Four trials have examined varying doses of surfactant;[103,206-208] whilst there were greater early improvements in oxygenation and ventilation, and some reductions in air leaks and neonatal mortality when using doses around 100 mg/kg compared with the smaller doses, larger doses did not appear to confer any additional advantage. Oxygenation and ventilation changes more rapidly after a surfactant dose of 200 mg/kg compared with 100 mg/kg but in a porcine model of RDS these changes were associated with greater changes in systemic and cerebral blood flows.[209] At present the optimum dose of surfactant would seem to be 100 mg/kg.

3.4 Methods of Administration

3.4.1 Bolus Administration

Currently available surfactants are administered as a bolus intratracheal injection, relying on the spreading phenomena of the surfactant itself to carry surfactant to the distal aerated airways.[210] Surfactant spreads across the air-tissue interface at twice the rate of saline[211] largely due to the surfactant proteins SP-B and SP-C.[212] Yet, surfactant spreading between different lobes of the lung has not been shown to occur in an animal model of RDS.[213] This can lead to inhomogeneity in the distribution of surfactant in the lung,[214] especially where the lung is atelectatic,[215] resulting in lung damage. Early surfactant administration,[215] the presence of fetal lung fluid[215] and increasing surfactant volume[214,216] have all been shown to decrease this inhomogeneity in surfactant distribution.

There are also concerns that bolus administration can lead to fluctuations in both systemic and pulmonary arterial blood pressure, which, in turn, may increase the risk of intraventricular hemorrhage (IVH); one placebo-controlled trial of beractant was halted because of an increase in IVH.[128] Surfactant therapy causes a number of changes in both pulmonary and systemic circulations.[217,218] Most studies report a reduction in systemic blood pressure but pulmonary arterial blood pressure has been shown in various studies to be either increased,[219] decreased[218,220] or unaffected.[217] These changes appear to be due to the effect of surfactant itself and not merely to the endotracheal administration of fluid.[218]

The logical approach of administering surfactant more slowly does not appear to improve homogeneity of spread. Segerer et al.[221,222] compared the efficacy of infusion of surfactant over 5 minutes and 1 hour with bolus administration. In both studies there were greater early improvements in ventilation and oxygenation with bolus administration which agrees with the finding in animal models that surfactant distribution is more homogeneous following bolus administration than after infusion.[223]

Further studies have modified the administration technique. Zola et al.[224] administered smaller boluses of beractant (1 ml/kg versus the standard 2 ml/kg aliquots). Whilst the two 2 ml/kg aliquots produced more reflux up the endotracheal tube, the four 1 ml/kg aliquots took longer to administer. There were no differences in the proportion of infants who had bradycardia and/or hypoxia during surfactant administration. Valls-i-Soler and the Spanish Surfactant Collaborative Group examined two other

techniques. In the first study,[155] a 'side hole' was used to administer poractant alfa over 1 minute but this did reduce the frequency of bradycardia and/or hypoxia. In the second study,[225] a dual lumen endotracheal tube, in contrast, statistically significantly reduced bradycardia and/or hypoxia.

3.4.2 Nebulization

Nebulized surfactant should theoretically have less cardiorespiratory adverse effects and has been shown to be more effective than bolus administration in an animal model of acute lung injury.[226] Other studies have shown it to be less effective[227] and to result in a large amount of wastage with less than 15% of surfactant administered being delivered to the lung.[228] Recovery of alveolar surfactant was 100 times greater after bolus administration than nebulization.[229] Studies of nebulized surfactant in neonatal populations have not shown any beneficial effect.[230,231]

3.4.3 Intra-Amniotic Administration

Intra-amniotic administration has been proposed as a method of delivering surfactant, potentially decreasing the inhomogeneity by delivering surfactant to a fluid-filled lung before the first breath. However, in a rabbit model of RDS there were no advantages over postnatal administration.[232] Limited experience in humans suggested technical difficulties of using ultrasound to guide a catheter to the fetal anterior nares and the use of a potentially toxic drug, aminophylline, in the mother may well be prohibitive.[233]

3.5 Current Administration Regimens

Exogenous surfactant is lost from the alveolus in several ways. Some surfactant is recycled and mixed with endogenous surfactant[234] while the rest is removed by alveolar macrophages or inactivated by serum proteins.[235] Turnover of alveolar phosphatidylcholine is approximately 13 hours.[236] Thus, if endogenous surfactant is not being made, additional doses of exogenous surfactant are required. Two issues that need to be answered are how many doses of surfactant should be given and the interval between doses.

3.5.1 How Many Doses of Surfactant Should Be Given?

Several trials have looked at this issue. Multiple doses are clearly better than single doses in most neonates[104,237] but no clear advantages were seen when more than two doses were routinely used.[100,105,107]

3.5.2 Intervals Between Doses

Early controlled trials of exogenous surfactant used a variety of dosing intervals, ranging from 1 hour (between the first and second doses of pumactant[18]) to 12 hours.[104,237] A variety of criteria were used for selecting which neonates received subsequent doses based on oxygen requirements,[126,129] whether or not the neonate remained ventilated,[98] and the use of the oxygenation index.[167] Although a variety of dosing schedules were developed during early placebo-controlled trials, most exogenous surfactants are currently administered at 12-hourly intervals. This correlates well with the turnover of DPPC,[236] but occasionally clinical benefit may be seen with more individualized treatment regimens.[238,239]

3.6 Does the Volume of Surfactant Matter?

Evidence from animal studies suggest that large volume surfactants are spread in a more homogeneous manner[214,216] and that homogeneity is important in determining clinical effectiveness. The potential disadvantages of larger volumes such as endotracheal tube obstruction and hypoxia have not been confirmed, these complications are reported to occur in 30 to 40% of infants irrespective of the type of surfactant used.

The only clinical trials comparing different volume surfactants are 'rescue' trials of poractant alfa (1.25 ml/kg or 2.5 ml/kg) compared with colfosceril palmitate (4 ml/kg)[115] and beractant (4 ml/kg).[133,172] Despite the fact that the former compared an animal-derived and a protein-free surfactant, there was a trend to higher mortality after poractant alfa. In studies using poractant alfa and beractant, there was a trend to higher mortality with beractant only when a higher dose of poractant was used. Both these results need to be interpreted in the light of different surfactants, and different amounts of phospholipids[133] being used. Further trials using different volumes of the same exogenous surfactant are required to answer this question.

3.7 Surfactant and Different Modes of Respiratory Support

High frequency oscillatory ventilation (HFOV) uses a higher mean airway pressure but with cycle volumes that are smaller than the tidal volume of the ventilated neonate. Compared with conventional ventilation, HFOV limited the development of proteinaceous exudates in the lungs of animals with RDS.[240-242] In neonates, early HFOV reduced the need for exogenous surfactant compared with conventional ventilation, although there were no long-term differences in pulmonary outcomes.[243] When HFOV and exogenous surfactant were used in combination there was a greater reduction in lung injury than if either had been used alone.[244] The reduced protein leak seen with HFOV prolongs the effectiveness of exogenous surfactant.[245] One problem with HFOV and surfactant is that HFOV has been shown to delay the

spread of surfactant from proximal to distal airways when compared with conventional ventilation.[246]

The early improvements in oxygenation after surfactant use are due to alveolar recruitment and improved functional residual capacity (FRC);[247] some improvement in lung volume may be due to distension of existing functional alveoli rather than previously atelectatic ones.[248] Continuous positive airways pressure (CPAP) also increases FRC and its use in the delivery room with or without surfactant has been shown to reduce the need for subsequent ventilation.[249] CPAP has also successfully been used to manage small preterm neonates with RDS,[250] and when combined with surfactant therapy, reduced the need for ventilation in infants with moderately severe RDS,[251] especially when administered early or prophylactically.[252,253] Unfortunately, these neonates still require intubation to administer the surfactant; success of this procedure and subsequent extubation can be operator dependent. More research is needed in this area before a viable alternative to intubation is available.

4. Long-Term Outcomes

The introduction of surfactant treatment was associated with a general reduction in mortality in neonates weighing between 601 to 1300g at birth[254] and a reduction in the overall neonatal and infant mortality in the US[255] comprising most likely improvements in both antenatal and postnatal care.[256] Although exogenous surfactant saves lives, there is no evidence, either from epidemiological data of 'pre-' and 'post-surfactant' eras[257,258] or from long-term outcome data from the controlled trials,[259-268] that surfactant increases the proportion of survivors with neurological impairment; some data show a decrease in respiratory morbidity among surfactant-treated infants during the first year of life.[260,263]

5. Economics of Surfactant Therapy in RDS

Concerns that surfactant might delay the deaths of some neonates with increased respiratory morbidity and support adding to the costs led to a number of studies examining the impact of surfactant therapy from an economic perspective.[269-278] Prophylactic surfactant therapy was more likely to show cost-benefits than rescue therapy in these studies but only short-term health service costs relating primarily to the duration of care in the nursery were examined; there may be additional long term costs to the healthcare system and to the family which need to be taken into account.[279]

Although surfactant is an expensive therapy at approximately $US500 per dose, these studies show that it is cost-effective in the developed world. In the developing countries, outcomes also reflect poorer antenatal care.[280] The cost of the surfactant may, in these countries, be more prohibitive and lead to its use in only selected cases.[281] Even when used in selected cases, surfactant use in neonates in developing countries remained cost effective.[282]

6. Conclusions

The discoveries leading to greater understanding of the nature and function of surfactant spread over most of the 20th century and have led to the widespread use of exogenous surfactants in RDS in preterm neonates. Since the introduction of surfactant, thousands of neonates have been treated and research into its characteristics, function and therapeutic efficacy has expanded exponentially.

Greater knowledge of the function of the components of endogenous surfactants, particularly the surfactant-associated proteins, helps us to better understand the limitations of existing exogenous surfactants in treating infants with RDS. Studies have shown surfactant is well tolerated and efficacious in RDS, but this in itself has raised other questions particularly with respect to CLD in survivors.

Synthetic surfactant proteins are beginning to provide viable therapeutic alternatives to animal-derived surfactants. These synthetic surfactants need to be compared with existing surfactants. The effectiveness of existing animal-derived surfactant products means that it will probably be difficult to demonstrate clear superiority of new synthetic surfactants over animal-derived surfactants in clinical trials. Nonetheless, the development of new synthetic surfactant substitutes (eliminating the risk of contamination with prions in products of animal origin) will be an important challenge for future research, particularly if the issue of CLD is to be addressed.

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