

Exogenous Surfactant Therapy in Newborn Infants

G K Suresh,*^{MD, DM, MS}, R F Soll,**^{MD}

Abstract

Exogenous surfactant therapy has an established role in the management of neonatal respiratory distress syndrome (RDS). This article summarises the current evidence on surfactant therapy. The use of surfactant for the treatment or prophylaxis of neonatal RDS results in a 30% to 65% relative reduction in the risk of pneumothorax and up to a 40% relative reduction in the risk of mortality. Adverse effects, of which pulmonary haemorrhage is of most concern, are infrequent and long-term follow-up studies of treated patients are reassuring. Natural surfactants have advantages over synthetic surfactants, including a lower frequency of pneumothorax and a lower mortality. Prophylactic administration of surfactant is preferred over 'rescue' administration, especially in infants of <30 weeks' gestation, as it decreases the risk of pneumothorax, pulmonary interstitial emphysema and neonatal mortality. Prophylaxis can be administered after initial resuscitation and stabilisation. In preterm infants who do not receive prophylactic surfactant, the first dose of surfactant should be administered as early as possible – early selective treatment decreases the risk of pneumothorax, pulmonary interstitial emphysema, chronic lung disease and neonatal mortality. A regimen of using multiple doses of surfactant if required has advantages over a single dose regimen. Exogenous surfactant therapy has also been used in neonatal respiratory disorders other than RDS. In trials in severe meconium aspiration syndrome, surfactant therapy reduced the need for extracorporeal membrane oxygenation. Its role in other disorders requires testing. The development and testing of newer surfactants is in progress.

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Introduction

Exogenous surfactant therapy is widely used in the management of neonatal respiratory distress syndrome (RDS) and may have a role in the management of other neonatal respiratory disorders as well. Numerous randomised controlled trials have been conducted in neonatology to study different aspects of surfactant therapy. In this article, we will review the published evidence on exogenous surfactant therapy in neonates, in order to identify clinical practices that are supported by the evidence and to understand the clinical impact of surfactant therapy.

Types of Surfactant

Two types of surfactant are available for exogenous therapy: surfactant derived from animal sources or 'natural' surfactant, and synthetic surfactant.

Natural Surfactant

The currently available natural surfactant preparations

are obtained from either bovine or porcine lungs. Beractant (Survanta) and Surfactant TA (Surfacten) are lipid extracts of bovine lung mince with added dipalmitoyl-phosphatidylcholine (DPPC), tripalmitoylglycerol and palmitic acid. Calf lung surfactant extract (CLSE, Infasurf), SF-RI1 (Alveofact) and Bovine Lipid Extract Surfactant (BLES) are bovine lung washes subjected to chloroform-methanol extraction. Porcine surfactant (poractant, Curosurf) is a porcine lung mince that has been subjected to chloroform-methanol extraction and further purified by liquid-gel chromatography. It consists of approximately 99% polar lipids (mainly phospholipids) and 1% hydrophobic, low molecular weight proteins [surfactant protein B (SP-B) and surfactant protein C (SP-C)].¹ All the natural surfactants contain SP-B and SP-C but the lung mince extracts (Survanta and Curosurf) contain less than 10% of the SP-B that is found in the lung-wash extracts (Infasurf, Alveofact and BLES).² The purification procedure including extraction with organic solvents removes the

* Assistant Professor

** Professor

Department of Pediatrics, Neonatal Division
University of Vermont College of Medicine
Burlington, Vermont, USA

Address for Reprints: Dr Gautham K Suresh, Department of Pediatrics, Neonatal Division, Given Building, University of Vermont College of Medicine, Burlington, VT 05405, USA.

E-mail: gautham.suresh@vtmednet.org

hydrophilic proteins SP-A and SP-D, leaving a material containing only lipids and small amounts of hydrophobic proteins. Poractant, which is further purified by liquid gel chromatography, contains only polar lipids and about 1% hydrophobic proteins (SP-B and SP-C in an approximate molar ratio of 1:2).³ None of the commercial preparations contain SP-A.²

Synthetic Surfactant

The predominant phospholipid found in all naturally occurring lung surfactants is DPPC. Therefore, it is not surprising that the principal surface-active agent in synthetic surfactants is DPPC. Other components may be added to facilitate surface adsorption. The two widely tested and commercially available synthetic surfactants lack many of the components of natural surfactant. Colfosceril palmitate, hexadecanol, tyloxapol (Exosurf) consists of 85% DPPC, 9% hexadecanol and 6% tyloxapol (a spreading agent). Artificial lung expanding compound (Pumactant) is a 7:3 mixture of DPPC and phosphatidyl glycerol. Two new synthetic surfactants are currently in a phase of development and testing. Lucinactant (Surfaxin) is a synthetic preparation that contains a peptide called KL4 (sinapultide), a mimic of SP-B. KL4 is a 21-residue peptide consisting of repeated units of four hydrophobic leucine (L) residues, bounded by basic polar lysine (K) residues. It is combined with DPPC, palmitoyl oleoyl-phosphatidyl glycerol and palmitic acid.^{4,5} Another synthetic surfactant, rSP-C surfactant (Venticute) contains a recombinant form of SP-C, along with DPPC, palmitoyl oleoylphosphatidyl glycerol, palmitic acid and calcium chloride.^{6,7} The recombinant surfactant protein C in this preparation (rSP-C) is an analogue of the human surfactant protein SP-C.

Effects of Surfactant Therapy

Immediate Pulmonary Effects of Surfactant Therapy

Exogenous surfactant therapy leads to rapid improvement in oxygenation, decrease in mechanical ventilator settings and an increase in the functional residual capacity, followed by a slower and variable increase in lung compliance.⁸⁻¹⁰ A decrease in pulmonary ventilation-perfusion mismatch has also been reported.¹¹⁻¹³ Pulmonary blood flow, following surfactant administration, has been reported to be unchanged in some studies¹⁴⁻¹⁶ and increased in others.¹⁷⁻²⁰ It is uncertain whether these changes in pulmonary circulation are related to ventilation practices, blood gas status or to surfactant itself. Treatment with exogenous surfactant also results in radiological improvement, with chest radiographs after treatment often (but not always) showing a decrease in the signs of RDS. This clearing of the lungs can be uniform, patchy or asymmetric, sometimes with disproportionate improvement of radiologic changes in the right lung.²¹⁻²⁵

Clinical Trials of Surfactant Therapy Compared to Placebo or No Therapy

Systematic reviews of randomised trials from the late 1980s and early 1990s²⁶⁻²⁹ show that, compared to placebo or no therapy, surfactant treatment or prophylaxis (with either natural or synthetic surfactant) decreases the risk of pneumothorax and decreases mortality. Estimates from the meta-analyses indicate that there is a 30% to 65% relative reduction in the risk of pneumothorax and up to a 40% relative reduction in the risk of mortality. There were no consistent effects on other clinical outcomes such as chronic lung disease, patent ductus arteriosus and intraventricular haemorrhage. In addition to these randomised trials, studies comparing the outcomes of very-low-birth-weight (VLBW) infants before and after the introduction of surfactant therapy demonstrated a decrease in mortality and morbidity for VLBW infants after the introduction of surfactant therapy.³⁰⁻³³ However, this decline in mortality has not been universally observed. In particular, racial differences in this decline in mortality have been reported. In one study, the overall neonatal mortality for Black VLBW infants did not change after the introduction of surfactant therapy³⁰ and in another study, declines in neonatal mortality risks caused by RDS and all respiratory causes were greater for non-Hispanic White VLBW infants than for Black VLBW infants.³⁴

Long-term Outcomes after Surfactant Therapy

For both synthetic and natural surfactants, 'long-term' outcomes have been reported predominantly in the first 3 years of life, with very few reports of outcomes at school-age or later. Long-term outcomes after surfactant therapy have been better studied for synthetic surfactant than for natural surfactant. Given these limitations, the evidence suggests that not only do more infants survive from surfactant therapy but they are also at no selective disadvantage for neurodevelopmental sequelae due to the surfactant therapy.

Neurodevelopmental Outcomes

No significant differences have been reported in the long-term neurodevelopmental outcomes of infants treated with surfactant compared to those treated with placebo, either with synthetic surfactant,³⁵⁻³⁷ or natural surfactant.³⁸⁻⁴³ A recent systematic review of 13 randomised trials concluded that surfactant therapy increases survival without an increase in subsequent morbidity at 1 and 2 years of age.⁴⁴

Respiratory Outcomes

Compared to infants treated with placebo, infants treated with surfactant in the neonatal period are reported to have

either improved⁴⁵⁻⁴⁷ or equivalent results⁴⁸⁻⁵⁰ on pulmonary function testing.

Adverse Effects of Surfactant Therapy

Few serious adverse effects have been reported in association with surfactant therapy. Acute adverse effects include transient hypoxia and bradycardia due to acute airway obstruction immediately following surfactant instillation,^{51,52} reflux of surfactant into the pharynx from the endotracheal tube, increase in transcutaneous carbon dioxide tension, tachycardia, gagging and mucous plugging of the endotracheal tube. These complications of surfactant administration generally respond to a slower rate of surfactant administration or to an increase the airway pressure or FiO₂ during administration. Rapid improvement in oxygenation after surfactant administration necessitates close monitoring and appropriate reduction of ventilatory parameters. Several authors have reported a transient decrease in blood pressure, a transient decrease in cerebral blood flow velocity a transient decrease in cerebral oxyhaemoglobin concentration and a transient decrease in cerebral activity on amplitude-integrated electroencephalography immediately after surfactant administration.^{53,53-58} The clinical significance of these findings is uncertain.

The one worrisome risk associated with surfactant therapy is an increased risk of pulmonary haemorrhage. In a meta-analysis of randomised trials of natural and synthetic surfactant therapy, there was a 47% relative increase in the frequency of pulmonary haemorrhage (pooled relative risk 1.47, 95% CI 1.05, 2.07).⁵⁹ However, the overall incidence of pulmonary haemorrhage was low (<5%) and the absolute magnitude of the increased risk is small. The occurrence of pulmonary haemorrhage may be related to the presence of a patent ductus arteriosus⁶⁰ or to direct cytotoxicity, which has been demonstrated in *in vitro* studies.⁶¹

Choice of Surfactant Preparation

Natural versus Synthetic Surfactant

Although both synthetic and natural surfactants are effective, their composition is significantly different. Natural surfactant extracts contain surfactant specific proteins that aid in surfactant adsorption and resist surfactant inactivation. A systematic review⁶² of 11 randomised trials that studied the effects of natural versus synthetic surfactant for the treatment of RDS is available.⁶³⁻⁷³ The results of the meta-analysis are summarised in Table I. The results of the meta-analyses are presented as the pooled estimates of relative risk (RR) and absolute risk difference (ARD), with 95% confidence intervals (CI). Compared to synthetic surfactant, treatment with natural surfactant extracts resulted in a decrease in the frequency of pneumothorax (pooled RR 0.63, 95% CI 0.53, 0.75; pooled ARD -4%, 95% CI -6%, -3%) and a decreased mortality (pooled RR 0.86, 95% CI 0.76, 0.98; pooled ARD -2%, 95% CI -5%, 0%). Natural surfactant extract was associated with a marginal increase in the risk of intraventricular haemorrhage (typical RR 1.09, 95% CI 1.00, 1.19; pooled ARD 3%, 95% CI 0%, 6%), but no increase in grade 3 to 4 intraventricular haemorrhage (pooled RR 1.08, 95% CI 0.92, 1.28; typical ARD 1%, 95% CI -1%, 3%). The meta-analyses support a marginal decrease in the risk of bronchopulmonary dysplasia or mortality associated with the use of natural surfactant preparations (pooled RR 0.95, 95% CI 0.90, 1.01; pooled ARD -3%, 95% CI -6%, 0%). No other relevant differences in outcome are noted. In addition to these benefits, natural surfactants have a more rapid onset of action, allowing ventilator settings and inspired oxygen concentrations to be lowered more quickly than with synthetic surfactant.^{67,70,74,75}

Comparison of Different Types of Natural Surfactants

Published literature on clinical outcomes does not provide

TABLE I: META-ANALYSIS OF 11 RANDOMISED TRIALS COMPARING NATURAL VERSUS SYNTHETIC SURFACTANT

Outcome (No. of trials)	No. of participants	Pooled risk difference [95% CI]	Pooled relative risk [95% CI]
Pneumothorax (9)	4550	-0.04 [-0.06, -0.03]	0.63 [0.53, 0.75]
Patent ductus arteriosus (7)	3283	-0.01 [-0.04, 0.02]	0.98 [0.91, 1.06]
Sepsis (8)	4413	0.0 [-0.02, 0.02]	1.00 [0.90, 1.12]
Intraventricular haemorrhage (7)	4220	0.03 [0.00, 0.06]	1.09 [1.00, 1.19]
Severe intraventricular haemorrhage, grades 3 or 4 (8)	4202	0.01 [-0.01, 0.03]	1.08 [0.92, 1.28]
Retinopathy of prematurity (4)	2396	-0.03 [-0.07, 0.01]	0.95 [0.88, 1.01]
Bronchopulmonary dysplasia (8)	3515	0.01 [-0.02, 0.04]	1.02 [0.93, 1.11]
Chronic lung disease (5)	3179	0.00 [-0.03, 0.03]	1.01 [0.90, 1.12]
Mortality (10)	4588	-0.02 [-0.05, 0.00]	0.86 [0.76, 0.98]
Chronic lung disease or death	2565	-0.01 [-0.05, 0.03]	0.98 [0.90, 1.06]

From: Soll R F, Blanco F. Natural surfactant extract versus synthetic surfactant for neonatal respiratory distress syndrome. Cochrane Database Syst Rev 2001; (2):CD000144.

any evidence to establish the superiority of one or more natural surfactant products over others. Two randomised trials have compared the efficacy and adverse effects of different natural surfactant products. In a comparison of beractant (Survanta) and calf lung surfactant extract (Infasurf),⁷⁶ there were no differences detected between the two groups in the frequency of air leaks, complications associated with dosing, complications of prematurity, mortality or survival without chronic lung disease. However, some differences were noted among sub-groups of infants. Among infants treated for established RDS, those who received calf lung surfactant extract had a significantly longer interval between doses, a lower inspired oxygen concentration and a lower mean airway pressure in the first 48 hours of life than infants treated with beractant. Among infants in whom these surfactants were used in a preventive strategy, mortality in infants with a birth weight <600 g was significantly higher with calf lung surfactant extract than with beractant. In another small unblinded trial comparing poractant and beractant,⁷⁷ infants treated with poractant had a more rapid improvement in oxygenation and reduced ventilator requirements up to 24 hours after the start of treatment compared to infants treated with beractant. This trial did not have enough power to detect true differences in important clinical outcomes between the two groups. In addition, the apparent superiority of poractant over beractant has two alternative explanations – the trial investigators were more experienced with poractant than beractant and a higher dose of phospholipids was used with poractant (200 mg/kg) than with beractant (100 mg/kg).

Timing Of Surfactant Administration

Prophylactic versus 'Rescue' Surfactant Administration

The rationale for prophylactic administration of surfactant is provided by the observation that in animal studies, a more uniform and homogenous distribution of surfactant is achieved when it is administered into a fluid-filled lung^{78,79} and by the belief that administration of surfactant into a previously unventilated or minimally ventilated lung will diminish acute lung injury. In animal models, even brief (15 to 30 minutes) periods of mechanical ventilation prior to surfactant administration have been shown to cause acute lung injury resulting in alveolar-capillary damage, leakage of proteinaceous fluid into the alveolar space and release of inflammatory mediators⁸⁰ and to decrease the subsequent response to surfactant replacement.⁸¹ Surfactant-deficient animals, which receive assisted ventilation, develop necrosis and desquamation of the bronchiolar epithelium as early as 5 minutes after onset of ventilation.⁸²

Eight randomised controlled trials compared the effects of prophylactic surfactant administration to surfactant treatment of established RDS.⁸³⁻⁹⁰ All these trials used natural surfactant preparations. Prophylactic surfactant was administered at different times but before 15 minutes of age. The results of the meta-analysis of these trials from a systematic review⁹¹ are summarised in Table II. Compared to surfactant treatment of established RDS, prophylactic administration of surfactant resulted in a decrease in the risk of pneumothorax (pooled RR 0.62, 95% CI 0.42, 0.89; pooled ARD -2%, 95% CI -4%, -1%), a decrease in the risk of pulmonary interstitial emphysema (pooled RR 0.54,

TABLE II: META-ANALYSIS OF 8 RANDOMISED TRIALS COMPARING PROPHYLACTIC AND RESCUE TREATMENT WITH NATURAL SURFACTANT

Outcome (No. of trials)	No. of participants	Pooled risk difference [95% CI]	Pooled relative risk [95% CI]
Pneumothorax (6)	2515	-0.02 [-0.04, -0.01]	0.62 [0.42, 0.89]
Pulmonary interstitial emphysema (5)	2037	-0.03 [-0.04, -0.01]	0.54 [0.36, 0.82]
Necrotising enterocolitis (5)	2368	0 [-0.02, 0.02]	1.01 [0.73, 1.40]
Patent ductus arteriosus (6)	2515	-0.01 [-0.04, 0.02]	0.96 [0.85, 1.09]
Intraventricular haemorrhage (7)	2508	-0.03 [-0.06, 0.01]	0.92 [0.82, 1.03]
Severe intraventricular haemorrhage (7)	2508	-0.02 [-0.04, 0.01]	0.84 [0.66, 1.06]
Bronchopulmonary dysplasia (8)	2816	-0.01 [-0.03, 0.02]	0.96 [0.82, 1.12]
Neonatal mortality (7)	2613	-0.05 [-0.07, -0.02]	0.61 [0.48, 0.77]
Mortality prior to hospital discharge (5)	1207	-0.05 [-0.09, -0.01]	0.75 [0.59, 0.96]
Bronchopulmonary dysplasia or death (8)	2816	-0.04 [-0.07, -0.01]	0.85 [0.76, 0.95]
Retinopathy of prematurity (4)	1919	0.00 [-0.01, 0.02]	1.09 [0.72, 1.66]
Retinopathy of prematurity, stage 2-4 (2)	390	0.00 [-0.05, 0.05]	0.97 [0.45, 2.10]
Neonatal mortality in infants <30 weeks' gestation (7)	1822	-0.06 [-0.09, -0.03]	0.62 [0.49, 0.78]
Bronchopulmonary dysplasia or death in infants <30 weeks' gestation (8)	2025	-0.05 [-0.09, -0.01]	0.87 [0.77, 0.97]

From: Soll R F, Morley C J. Prophylactic versus selective use of surfactant in preventing morbidity and mortality in preterm infants. Cochrane Database Syst Rev 2001; (2):CD000510.

95% CI 0.36, 0.82; pooled ARD -3%, 95% CI -4%, -1%), a reduction in the risk of neonatal mortality (pooled RR 0.61, 95% CI 0.48, 0.77; pooled ARD -5%, 95% CI -7%, -2%) and a trend towards a decrease in the risk of intraventricular haemorrhage (pooled RR 0.92, 95% CI 0.82, 1.03; pooled ARD -3%, 95% CI -6%, 1%). Because of the greater risk of RDS and mortality with decreasing gestational age, the benefits of prophylactic administration compared to selective administration were of greater magnitude. The meta-analysis demonstrates that compared to selective administration, prophylactic administration of natural surfactant to infants less than 30 weeks gestation resulted in a reduction in neonatal mortality (pooled RR 0.62, 95% CI 0.49, 0.78; pooled ARD -6%, 95% CI -9%, -3%) and a reduction in the combined outcome of bronchopulmonary dysplasia or death (pooled RR 0.87, 95% CI 0.77, 0.97; pooled ARD -5%, 95% CI -9%, -1%). These findings have to be interpreted in light of the fact that the mean time of administration of surfactant in the selective treatment groups ranged from 1.5 to 7.4 hours. Furthermore, the use of antenatal steroids during the period when these trials were conducted was not as high as it is currently. Therefore the magnitude of effect of prophylactic surfactant in current practice may not be as high as it was in the original trials. Randomised trials to compare the effects of prophylactic surfactant administration to very early selective administration, for example at 30 to 60 minutes of life are required.

Two studies compared the long-term outcomes of infants treated with prophylactic surfactant to those treated with a 'rescue' strategy. In one, there were no differences at school-age in neurodevelopmental outcome or in the results of pulmonary function testing between the two groups,

although infants who had received prophylactic surfactant showed fewer clinical pulmonary problems than those that received rescue treatment.⁹² In the second study, in which there was significant loss of infants to follow-up (and therefore a high likelihood of attrition bias), the mean scores on the Bayley scales of Infant Development at 12 months adjusted age were higher in the rescue group than in the prophylactic group.⁹³

The benefits of prophylactic surfactant have to be weighed against the fact that surfactant prophylaxis results in the treatment of certain infants who do not have RDS (and therefore do not require surfactant). A prophylaxis strategy for a given category of infants will also result in the intubation of certain infants who would have otherwise not been intubated. At what point do the potential benefits of decreased mortality, decreased pneumothorax and decreased lung injury from prophylactic surfactant exceed the potential risks of endotracheal intubation and the costs of surfactant dosing to infants who would not have required it? We believe that, based on the evidence, this threshold is around 30 weeks' gestation. Others have proposed a gestation of 29 weeks^{2,94} or 28 weeks.⁹⁵

Preventive versus Post-ventilatory Prophylactic Surfactant Administration

Initial studies, using prophylactic surfactant, administered the drug as an immediate bolus after intubating the infants rapidly after birth (i.e., "before the first breath"). This approach delays the initiation of neonatal resuscitation, including positive pressure ventilation, and is associated with a risk for surfactant delivery into the right main stem bronchus or oesophagus. Based on a randomised trial that showed that prophylaxis may be administered in small

TABLE III: META-ANALYSIS OF 4 RANDOMISED TRIALS COMPARING EARLY AND DELAYED SELECTIVE SURFACTANT TREATMENT

Outcome (No. of trials)	No. of participants	Pooled risk difference [95% CI]	Pooled relative risk [95% CI]
Pneumothorax (3)	3427	-0.05 [-0.08, -0.03]	0.70 [0.59, 0.82]
Patent ductus arteriosus (4)	3459	0.01 [-0.02, 0.04]	1.03 [0.92, 1.15]
Pulmonary interstitial emphysema (2)	737	-0.06 [-0.1, -0.01]	0.63 [0.43, 0.93]
Pulmonary haemorrhage (2)	3007	-0.0 [-0.02, 0.02]	0.99 [0.73, 1.34]
Necrotising enterocolitis (3)	3427	0.00 [-0.01, 0.02]	1.08 [0.77, 1.51]
Retinopathy of prematurity stage 3 or greater (2)	3007	0.00 [-0.01, 0.01]	1.06 [0.58, 1.91]
Intraventricular haemorrhage (any) (1)	32	0.0 [-0.30, 0.3]	1.00 [0.30, 3.32]
Intraventricular haemorrhage (severe) (2)	3007	-0.01 [-0.03, 0.02]	0.97 [0.83, 1.14]
Bronchopulmonary dysplasia (3)	3039	-0.01 [-0.05, 0.02]	0.97 [0.88, 1.06]
Chronic lung disease (2)	3007	-0.03 [-0.05, -0.01]	0.70 [0.55, 0.88]
Neonatal mortality (4)	3459	-0.03 [-0.06, -0.00]	0.87 [0.77, 0.99]
BPD or death at 28 days (3)	3039	-0.04 [-0.07, -0.0]	0.94 [0.88, 1.00]
Chronic lung disease or death (2)	3007	-0.06 [-0.09, -0.03]	0.84 [0.75, 0.93]
Mortality at discharge (3)	3039	-0.03 [-0.06, 0.0]	0.90 [0.79, 1.01]

From: Yost C C, Soll R F. Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome. Cochrane Database Syst Rev 2000; (2):CD001456.

aliquots soon after resuscitation and confirmation of endotracheal tube position, with equivalent or greater efficacy than “first breath” administration,⁹⁶ prophylactic surfactant should be administered after initial resuscitation and stabilisation of the infant at birth. Administration prior to the “first breath” is unnecessary.

Early versus Late Treatment of Established RDS

In preterm infants who do not receive prophylaxis, many of the same arguments in support of prophylactic surfactant administration are also supportive of early surfactant treatment of established RDS. Four randomised controlled trials⁹⁷⁻¹⁰⁰ have evaluated early versus delayed selective surfactant administration. The results of these trials have been summarised in a systematic review.¹⁰¹ Early administration of surfactant, in these trials, consisted of administration of the first dose of surfactant within the first 30 minutes, within the first hour or within the first 2 hours of life. Two of these studies used natural surfactants and two used synthetic surfactant. The results of the meta-analysis of these studies are summarised in Table III. Early selective treatment resulted in a decrease in the risk of pneumothorax (pooled RR 0.70, 95% CI 0.59, 0.82; pooled ARD -5%, 95% CI -8%, -3%), a decrease in the risk of pulmonary interstitial emphysema (pooled RR 0.63, 95% CI 0.43, 0.93; pooled ARD -6%, 95% CI -10%, -1%), a decrease in the risk of chronic lung disease (requirement for supplemental oxygen at 36 weeks' gestation), pooled RR 0.70, 95% CI 0.55, 0.88; pooled ARD -3%, 95% CI -5%, -1%) and a decrease in the risk of neonatal mortality (pooled RR 0.87, 95% CI 0.77, 0.99; pooled ARD -3%, 95% CI -6%, 0%). Therefore in preterm infants who do not receive prophylactic surfactant, the first dose of surfactant should be administered as early as possible. Outborn infants are at highest risk of delayed administration. Tertiary referral units accepting outborn infants should attempt to develop systems to ensure the administration of surfactant as early as possible to these infants, either by the transporting team or, if appropriate, by the referring hospital. In inborn infants, delays in administration of surfactant occur if other admission procedures such as umbilical catheter placement, chest radiographs and nursing procedures are allowed to take precedence over surfactant dosing soon after birth. Surfactant administration should be given priority over other admission procedures.

Repeated Administration of Surfactant

Single versus Multiple Doses of Surfactant

Many of the initial trials of surfactant therapy tested a single dose of surfactant. However, surfactant may become rapidly metabolised and functional inactivation of surfactant can result from the action of soluble proteins and other

factors in the small airways and alveoli.¹⁰² Multiple doses of surfactant are thought to be useful because they can overcome such inactivation. The results of two randomised controlled trials that compared multiple dosing regimens to single dose regimens of natural surfactant extract for treatment of established RDS^{103,104} have been evaluated in a systematic review.¹⁰⁵ Approximately 70% of the infants randomised to the multiple dose regimen received multiple doses. The meta-analysis supports a decreased risk of pneumothorax associated with multiple dose surfactant therapy (pooled RR 0.51, 95% CI 0.30, 0.88; pooled ARD -9%, 95% CI -15%, -2%). There was also a trend towards decreased mortality (pooled RR 0.63, 95% CI 0.39, 1.02; pooled ARD -7%, 95% CI -14%, 0%). No differences were detected in other clinical outcomes. No complications associated with multiple dose treatment were reported in these trials. In a third study, in which synthetic surfactant was used in a prophylactic manner, the use of two doses of surfactant in addition to a prophylactic dose lead to a decrease in mortality, respiratory support, necrotising enterocolitis and other outcomes when compared to a single prophylactic dose.¹⁰⁶ In the OSIRIS trial,¹⁰⁰ which used synthetic surfactant, a two-dose treatment schedule was found to be equivalent to a treatment schedule permitting up to four doses of surfactant.

Criteria for Repeat Doses of Surfactant

The use of a higher threshold for retreatment with surfactant appears to be as effective as a low threshold and can lead to significant savings in costs of the drug. The criteria for administration of repeat doses of surfactant have been addressed by two studies, both of which used natural surfactant. In one study,¹⁰⁷ the retreatment criteria compared were an increase in the fraction of inspired oxygen by 0.1 over the lowest baseline value (standard retreatment) versus a sustained increase of just 0.01 (liberal retreatment). There were no differences in complications of prematurity or duration of respiratory support. However, short-term benefits in oxygen requirement and ventilatory support were noted in the liberal retreatment group. In another study,¹⁰⁸ retreatment at a low threshold ($\text{FiO}_2 > 30\%$, still requiring endotracheal intubation) was compared to retreatment at a high threshold ($\text{FiO}_2 > 40\%$, mean airway pressure $> 7 \text{ cm H}_2\text{O}$). Again, there were minor short-term benefits to using a low threshold with no differences in major clinical outcomes. However, in a sub-group of infants with RDS complicated by perinatal compromise or infection, infants in the high threshold group had a trend toward higher mortality than the low-threshold group. Based on current evidence, it appears appropriate to use persistent or worsening signs of RDS as criteria for retreatment with surfactant. It is uncertain whether a low threshold strategy should be used in certain sub-groups of

infants or with certain preparations of surfactant.

Promoting Evidence-based Surfactant Practice in Preterm Infants

In spite of the evidence demonstrating that prophylactic surfactant administration has advantages over later, selective administration and that administration of surfactant before 2 hours of life is better than after 2 hours, data from the Vermont Oxford Network show a gap between the evidence and the practice. An analysis of data for nearly 29,000 infants 23 to 29 weeks gestation from 296 neonatal intensive care units in 1998 and 1999¹⁰⁹ revealed that the first dose of surfactant was given at a median of 53 minutes after birth. Of those given surfactant, the first dose was given within 15 minutes of birth in only 25% and over 2 hours in 24%. Ten per cent of infants were first treated more than 225 minutes after birth. Outborn infants were treated later than inborn infants (median time 83 versus 45 minutes). The time of the first dose varied markedly among hospitals.

Horbar et al¹¹⁰ recently conducted a cluster-randomised trial, with hospitals as the units of intervention, to test the efficacy of a multi-faceted intervention intended to close this gap in surfactant practice. This multi-faceted intervention consisted of individualised feedback to NICUs on the timing of surfactant administration in their units. A special workshop provided training in quality improvement methods and teams were exposed to the Cochrane systematic reviews on surfactant; ongoing support from project faculty was through an email discussion list and periodic conference calls. In this trial, infants at intervention hospitals received their first dose of surfactant sooner after birth than those in control hospitals (median: 21 versus 78 minutes, $P < 0.001$), were more likely to receive their first dose of surfactant in the delivery room (54.7% versus 18.2%, $P < 0.001$), and were less likely to receive it more than 2 hours after birth (9.4% versus 24.8%, $P < 0.001$). This trial suggests that further improvements in outcomes of surfactant therapy may not result just from improvements in the types of surfactant used. Instead, they may result from improvements in the process and methods of surfactant usage within neonatal units and from the promotion of evidence-based surfactant therapy in neonatal units where surfactant practices are sub-optimal.

Exogenous Surfactant Therapy for Conditions Other Than RDS

Meconium Aspiration Syndrome (MAS)

In vitro studies¹¹¹ and animal studies¹¹² have demonstrated that meconium inhibits surfactant function and is likely to be partially responsible for alveolar collapse in MAS. Components of meconium that may contribute to altered surfactant function include proteolytic enzymes, free fatty

acids, phospholipases, bile salts, blood, lanugo, squamous cells, bilirubin, proteins, steroid compounds, cholesterol and triglycerides.¹¹³ Exogenous surfactant treatment of human neonates with MAS has been reported in a few non-controlled studies.¹¹⁴⁻¹¹⁷ A randomised trial, in infants <34 weeks' gestation with severe respiratory failure on extracorporeal membrane oxygenation (ECMO) (including infants with MAS), showed that infants treated with beractant (Survanta) had improved lung function, a shorter duration of ECMO and fewer complications after ECMO.¹¹⁸

A systematic review of two randomised controlled trials^{119,120} evaluated the effect of beractant (Survanta) administration in term infants with MAS.¹²¹ In one trial,¹¹⁹ infants treated with surfactant had a fewer pneumothoraces (RR 0.09, 95% CI 0.01, 1.54, ARD -25%, 95% CI -45%, -5%), improved oxygenation and shorter durations of ventilation and hospitalisation. Both trials reported a decrease in the number of infants receiving ECMO. A meta-analysis of these trials supports a significant reduction in the risk of requiring ECMO (pooled RR 0.64, 95% CI 0.46, 0.91 pooled ARD -17%, 95% CI -30%, -4%). No difference was noted in overall mortality (pooled RR 1.86 95% CI 0.35, 9.89, pooled ARD 2% 95% CI -3%, 7%).

In conclusion, the use of exogenous surfactant therapy in infants with severe MAS is likely to be beneficial. Multiple doses are usually required in such infants. Only natural surfactants have been tested in human clinical trials in this setting and the efficacy of synthetic surfactants is unknown. Each dose should be administered cautiously, with close cardio-respiratory and oxygen saturation monitoring, in case pre-existing airway obstruction from meconium is aggravated by surfactant. Treatment of MAS by lavage with surfactant instead of bolus administration has been tried in animal models^{5,122-124} and human infants¹²⁵⁻¹²⁷ and is promising, but requires further research before it can be recommended.

Other Neonatal Respiratory Disorders

There are anecdotal reports or case series of the use of exogenous surfactant therapy in human infants for the management of pulmonary haemorrhage,¹²⁸ neonatal pneumonia,^{129,130} and congenital diaphragmatic hernia.^{131,132} However, the efficacy of surfactant in these conditions is uncertain and its routine use in these conditions cannot be recommended. Because exogenous surfactant therapy is successful in the treatment of neonatal RDS, it has been proposed as a treatment for patients with acute lung injury and the acute RDS (ARDS). ARDS has been reported to occur in term neonates.^{133,134} There are no randomised trials of exogenous surfactant therapy specifically for ARDS in neonates. However, it is often difficult to reliably distinguish ARDS from RDS due to surfactant deficiency. Because of

this, and based on the pathophysiologic, clinical and radiologic similarities between the two conditions, we believe that it is reasonable to provide exogenous surfactant therapy to term infants with a clinico-radiologic picture of ARDS (severe respiratory failure with pulmonary opacification and air bronchograms on chest radiographs).

Conclusions

With exogenous surfactant therapy there has been a significant advance in the management of preterm infants with RDS and has become established as a standard for the management of such infants. Both natural and synthetic surfactants lead to clinical improvement and decreased mortality, with natural surfactants having additional advantages over synthetic surfactants. The use of prophylactic surfactant, administered after initial stabilisation at birth, to infants at risk for RDS has benefits over 'rescue' surfactant given to treat infants with established RDS. In infants who do not receive prophylaxis, earlier treatment (before 2 hours) has benefits over later treatment. The use of multiple doses of surfactant is a superior strategy to the use of a single dose and the use of a higher threshold for retreatment appears to be as effective as a low threshold. Adverse effects of surfactant therapy are infrequent and usually not serious and the results of long-term follow-up of surfactant-treated neonates are reassuring. In addition to its role in the management of RDS, exogenous surfactant therapy may have a role in the management of MAS as well. Its role in the management of other neonatal respiratory disorders requires further investigation. The development and testing of new types of surfactants is in progress. Further research is also required on the optimal use of surfactant in conjunction with other respiratory interventions.

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