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A Risk-Benefit Assessment of Natural and Synthetic Exogenous Surfactants in the Management of Neonatal Respiratory Distress Syndrome

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Summary

Alveolar surfactant is central to pulmonary physiology. Quantitative and qualitative surfactant abnormalities appear to be the primary aetiological factors in neonatal respiratory distress syndrome (RDS) and exogenous replacement of

surfactant is a rational treatment. Available exogenous surfactants have a natural (mammal-derived lung surfactants) or synthetic origin.

Pharmacodynamic and clinical studies have demonstrated that exogenous surfactants immediately improve pulmonary distensibility and gas exchange; however, this is achieved more slowly and with more failures with synthetic surfactants. The ensuing advantageous haemodynamic effects are not so striking and they include an inconvenient increased left to right ductal shunt.

Two strategies of administration have been used: prophylactic or rescue therapy to treat declared RDS. All methods of instillation require intubation. In addition to the early benefits (improved gas exchange and reduced ventilatory support) the incidence of classical complications of RDS, especially air leak events, is decreased except for the uncommon problem of pulmonary haemorrhage. The incidence of bronchopulmonary dysplasia is neither uniformly nor significantly reduced although the severity appears to be lessened. The overall incidence of peri-intraventricular haemorrhages is not diminished although separate trials have shown a decreased rate. The most striking beneficial effect of exogenous surfactants is the increased survival (of about 40%) of treated very low birthweight neonates. A small number of adverse effects has been described.

The long term outcome of survivor neonates with RDS treated with surfactants versus control neonates with RDS not treated with surfactants is similar in terms of physical growth, at least as good in terms of respiratory status, with a similar or slightly better neurodevelopmental outcome. There is no clear benefit of exogenous surfactant therapy in extremely premature infants (<26 weeks gestational age, birthweight <750g).

The potential risks of contamination, inflammatory and immunogenic reaction and the inhalation of platelet activating factor remain a theoretical concern of surfactant therapy which has not been confirmed in clinical practice. The optimal timing of treatment favours prophylaxis over rescue treatment and early rescue treatment rather than delayed therapy. Meta-analyses suggest the clinical superiority of natural surfactant extracts over a synthetic one (colfosceril palmitate). The economic impact of surfactant therapy is favourable and the costs per quality-adjusted life year (QALY) for surviving surfactant treated infants are low.

In conclusion, the mid and long term benefit/risk ratio clearly favours the use of exogenous surfactants to prevent or to treat RDS in neonates who have a gestational age of >26 weeks or a birthweight of >750g, especially with the prophylactic strategy using natural surfactant extracts.

From birth, pulmonary surfactant is central to setting up, maintaining and stabilising lung gas volume. Surfactant lowers the surface tension of the air-liquid alveolar interface, thus preventing both alveolar collapse and the results of atelectasis upon gas exchange.[1]

Quantitative and qualitative abnormalities of surfactant are therefore a basic feature of neonatal respiratory diseases, especially respiratory distress syndrome (RDS) which is, at least in part, a consequence of primary surfactant deficiency. In spite of antenatal treatment with glucocorticoids, RDS remains the most frequent neonatal lung disease. RDS incidence is inversely correlated to gestational age, being 80% in neonates born <28 weeks after last menses, 60% at 28 to 29 weeks, 40% at 30 to 31 weeks, 20% at 32 weeks, 5% >32 weeks. The natural course of RDS results in high mortality, and later in respiratory morbidity and other sequelae. Since the 1970s, advances in general and respiratory care of premature neonates lowered RDS mortality from a former 70 to 20%.[2] But,

after scores of experimental studies beginning in the 1960s, the pioneering work by Fujiwara et al.[3] in 1980 marked a turning-point in clinical progress: first reporting that endotracheal instillation of a surface active substitute of natural surfactant extract was able to significantly improve gas exchange in 10 ventilated premature babies with severe RDS.[3] These results paved the way for numerous randomised clinical trials testing the efficiency and tolerability of various exogenous surfactants in preventing and/or treating RDS.[4-10]

In the 1990s, the worldwide routine use of exogenous surfactants to prevent and/or treat RDS has been associated with an increased survival of very low birthweight (VLBW) neonates. However, a true benefit is obtained only if survivors are not to be crippled by unfavourable and costly pulmonary, neurological and sensory sequelae.

This review aims to provide the prerequisite data to evaluate the real benefits versus possible adverse effects of exogenous surfactant therapy in RDS.

1. Exogenous Surfactant Preparations

To date, clinically available exogenous surfactants fit into 2 broad categories: the natural surfactant extracts (prepared from mammal lungs) and the synthetic surfactant preparations.[11]

Natural surfactant extracts are extracted with organic solvents from pulmonary lavage or minced lungs (bovine/porcine origin) or from human amniotic fluid; however, surfactants from this source are no longer in clinical use. Their phospholipid content is variable quantitatively and qualitatively as compared with the natural surfactant they come from. Some natural surfactant extracts [surfactant TA and beractant (Survanta®) are supplemented with extra phospholipids and fatty acids (dipalmitoylphosphatidylcholine, palmitic acid and tripalmitin). All of them retain diverse small amounts of specific hydrophobic proteins SP-B and SP-C.[12] The human-derived lung surfactant is the only one which also contains the specific hydrophilic glycoproteins SP-A and SP-D.

The synthetic surfactants have been designed to avoid the theoretical risks of natural surfactant extracts, i.e. exposure to foreign proteins and transmission of infectious organisms. They are made of similar synthetic phospholipids with/without addition of chemical components enhancing their surface active properties.

Tables I and II summarise the main characteristics of natural surfactant extracts and synthetic surfactant preparations used in clinical trials.

2. Pharmacodynamic Effects

2.1 Pulmonary Effects

Exogenous surfactants exert a potent effect upon the respiratory course of RDS. Natural sur-

Table I. Main characteristics of natural surfactant extract preparations used in clinical trials

Surfactant	Origin	Composition			Dose (mg/kg)	Volume (ml/kg)	Maximal no. of doses
		no. of phospholipids	no. of specific proteins	SP-B[a]			
Human[b]	Human/amniotic fluid	85	5 (SP-A,D,B,C)		60	3	4
S-TA (Surfacten®)	Bovine/minced lung	84[c]	1 (SP-B,C)	1	100	4	4
Beractant (Survanta®)	Bovine/minced lung	84[c]	1 (SP-B,C)	<0.1	100	4	4
CLSE (Infasurf®, bLES®)	Bovine/BAL	92	1 (SP-B,C)	1.7	90-105	3	3
Alveofact®	Bovine/BAL	88	1 (SP-B,C)	1.7	50	1.2	4
PLS (Curosurf®)	Porcine/minced lung	99	1 (SP-B,C)	0.2	200	2.5	3 (at 1.25 ml/kg)

a Given as a percentage related to the total amount of phospholipids (wt/wt).[12]

b No longer in clinical use.

c The final concentration is obtained by adding dipalmitoylphosphatidylcholine, palmitic acid and tripalmitin.

Abbreviations: BAL = bronchoalveolar lavage; CLSE = calf lung surfactant extract; PLS = porcine-derived lung surfactant; SP-A,D and SP-B,C = specific proteins A, D, B and C; wt = weight.

Table II. Main characteristics of synthetic surfactant preparations used in clinical trials

Surfactant	Composition (wt:wt)	Dose (mg/kg)	Volume (ml/kg)	Maximal no. of doses
Pumactant (ALEC)	DPPC + PG (7:3)	100	12[a]	4
'Turfsurf'[b]	DPPC + HDL (1:1)	25	1	1
Colfosceril palmitate	DPPC + hexadecanol + tyloxapol (13.5:1.5:1)	67.5	5	2

a Regardless of birthweight.

b No longer in clinical use.

Abbreviations: ALEC = artificial lung expanding compound; DPPC = dipalmitoylphosphatidylcholine; HDL = high-density lipoprotein; PG = phosphatidylglycerol; wt = weight.

factant extracts obtain a striking improvement of gas exchange within a few minutes of administration, extending for up to 48 hours [after instillation of a single 200 mg/kg dose of Curosurf®, a porcine-derived lung surfactant (PLS), for example[4]]. This allows the fraction of inspired oxygen (FiO_2) and ventilatory support to be decreased rapidly. Clinical studies have shown synthetic surfactants to have relatively slower onset of effects than their natural counterparts.[13]

Instillation of natural surfactant extract initiates a significant increase in the functional residual capacity (FRC) by an immediate 20 to 150%, then a progressive increase and a final steadiness[14-17] This is probably obtained by stabilising the formerly aerated alveoli rather than by recruiting new ones.[18] The FRC increase correlates well with the fast improvement in gas exchange. One synthetic surfactant, colfosceril palmitate (Exosurf® Neonatal™), has also been reported to influence FRC but with a later and smaller effect than with natural surfactant extract.[14]

Natural surfactant extracts obtain an early increase in pulmonary distensibility (measurement of total respiratory system static compliance, C_{rs}) within 2 hours of instillation. This increase is rapidly prominent (by 50% within 2 to 3 hours) and correlates well with the improvement of gas exchange.[19] Colfosceril palmitate has also been shown to result in a significant C_{rs} increase but only after 12 to 24 hours and on a smaller scale.[20,21]

The clinical data obtained from direct comparison studies involving natural surfactant extracts and colfosceril palmitate confirmed the difference in effectiveness shown by the above pharmacodynamic measurements.[22,23] The slower effect of synthetic surfactants has been shown to be caused mainly by their lack of SP-B and SP-C.[24] It might also be explained by the pre-exposure to the preterm lung they require to be 'activated' by the association with components of endogenous surfactant (as demonstrated in premature lambs with colfosceril palmitate[25]).

The instant effectiveness of exogenous surfactants is not uniform. Indeed, about 20% of neonates treated with a natural surfactant extract[26-29] and 50% of those treated with a synthetic one (colfosceril palmitate) do not exhibit any significant improvement,[30] furthermore about 30% of neonates who respond relapse rapidly. This may be caused by coexistent factors: pulmonary infection, acidosis, hypothermia, low systemic blood pressure, interstitial emphysema. Such additional complications must be treated in conjunction with surfactant therapy. In most cases these clinical factors aggravate pre-existing pulmonary oedema, further increasing the intra-alveolar amount of plasma proteins which inactivate the endogenous and exogenous surfactants.[12] Absence of improvement has been shown to herald a poor outcome of RDS, and in some cases RDS can be fatal.[30,31]

2.2 Cardiovascular and Cerebral Effects

Is surfactant a pulmonary vasodilator? If so, its haemodynamic effects should exceed those resulting from improved gas exchange alone. This question remains unanswered. Studies are difficult, therefore scarce, and the results to date are similar for natural surfactant extracts and synthetic surfactants. Following surfactant treatment, 2 studies using different Doppler techniques showed a fall in pulmonary blood pressure, but it was not clear if

this effect was caused by the surfactant itself.[32,33] RDS mostly features high rather than low pulmonary blood flow. After surfactant treatment, 3 further Doppler studies brought inconclusive evidence and it is concluded that total pulmonary blood flow is likely to remain grossly unchanged.[34-36]

The balance of flow through the large ductus arteriosus, which is present in the early hours after birth, depends on vascular resistances on the pulmonary versus systemic side of the ductus, which are mostly influenced by blood gases. Improvement of gas exchange brings both pulmonary vasodilation and systemic vasoconstriction, thus favouring an increase of the left to right ductal shunt (possibly overloading the pulmonary bed in a few cases).

Studies of systemic pressure and left ventricular output have only reported transient, low grade and irregular changes during and after surfactant instillation.[37-40]

The reactivity of autonomic cerebral blood flow (CBF) regulation to blood gases may explain some CBF disturbances during and after surfactant instillation. A rising partial arterial carbon dioxide pressure ($PaCO_2$) after rapid instillation may induce a transient rise in CBF in a few infants.[35] On the other hand, a delay in reducing ventilation (with hyperoxia/hypocarbia) may result in a decrease in CBF.[38] However, more direct investigations, either by near infrared spectroscopy or xenon clearance, showed small transient perturbations in cerebral blood volume and oxyhaemoglobin, but no important alterations of CBF and cerebral oxygen delivery.[41-44] It is possible to attenuate the initial disturbances of CBF by adjusting the dose of PLS[45] and even to suppress it by slowing the instillation rate of the synthetic surfactant colfosceril palmitate.[35]

A transient electroencephalogram depression has been known to occur after surfactant instillation in the proved absence of cerebral ischaemia, without relation to alterations of blood gases or systemic circulation, and its mechanism remains unsolved.[42,44,46-48]

3. Administration

3.1 Strategies

Two strategies have been tested and validated, one to prevent RDS (a prophylactic or preventive strategy) and one to treat it (a rescue or curative strategy).

In the prophylactic strategy, exogenous surfactant is instilled immediately during the first breaths in neonates who are considered to be at high risk of RDS (in practice, neonates with a gestational age of <31 weeks). These VLBW neonates at once undergo systematic intubation required for instillation, which is then performed before the first breath or within 15 minutes of birth.

The rescue strategy waits for the neonate to develop an obvious clinical and radiological signs of RDS. In these newborns the most frequently used criteria for treatment are: requirement for mechanical ventilation, $FiO_2 \geq 0.40$, and/or an arterial alveolar ratio (a/APO_2) <0.22.

3.2 Administration Methods

The surfactant instillation procedures have been empirically designed after animal experiments. All of them require tracheal intubation. As often as possible, a chest x-ray should be performed in the first instance to confirm the diagnosis of RDS, to exclude a pneumothorax (which should be drained before instillation), and to check the endotracheal tube level (lower end should be above carina to prevent selective unilateral instillation). The 'ideal' instillation must achieve a rapid improvement of gas exchange by the most uniform pulmonary distribution of exogenous surfactant so as to avoid baro/volotraumatisms with their short and mid term deleterious consequences. It should also not cause pulmonary or haemodynamic adverse effects, for example airway obstruction, bradycardia, drop of blood pressure, gas exchange imbalance.

As natural surfactant extracts have a fast effect it has been shown that bolus instillation is the technique of choice.[49] It can be performed: (i) by discontinuing mechanical ventilation, thereafter bag ventilation for some minutes (1 or 2) or directly

resuming the mechanical ventilation; (ii) without discontinuing ventilation, using an endotracheal tube adaptor with a side hole; (iii) either in the proximal part of the endotracheal tube, or in the distal part (with a catheter or feeding tube); (iv) dividing the total initial dose into 2 to 4 aliquots; and (v) with/without positioning the baby's head and thorax so as to ensure a uniform spread of surfactant.[50] A recent simplified technique (slow instillation of PLS for 1 minute via a catheter introduced in the side hole of an endotracheal connecting tube adaptor, without additional manoeuvres) produced similar results.[51]

For the synthetic surfactant colfosceril palmitate, which has to be given as a large volume 5 ml/kg/dose, the best method of administration seems to be a slow instillation into the tracheal tube through a special endotracheal tube adaptor with a side hole (provided in the packaging). The duration of instillation should not be less than 4 minutes and up to 30 minutes may be necessary.[52] In contrast, the synthetic surfactant pumactant (artificial lung expanding compound, ALEC) has been administered as a rapid bolus.

4. Therapeutic Efficacy and Tolerability

Tables III and IV summarise the data obtained from a literature based meta-analysis of 33 randomised controlled trials of prophylactic and rescue treatment with exogenous surfactants involving a total of nearly 6000 neonates.[53] The data demonstrate the efficacy of exogenous surfactants on the respiratory course of RDS, and attest to the ability of surfactants to decrease the severity of RDS and to reduce the main classical complications observed in RDS or prematurity. These benefits are enhanced by a remarkably good clinical tolerance.

The following subsections will deal mainly with the results obtained by use of exogenous surfactants in premature infants born at a gestational age of >26 weeks with a birthweight of >750g.

4.1 Pulmonary Outcomes

The incidence of pulmonary haemorrhage, an uncommon complication occurring in about 5% of neonates with RDS, has been found to be increased by 50% by the administration of exogenous surfactants.[54] However, this increased incidence of pulmonary haemorrhage was only significant for prophylaxis with the synthetic surfactant colfosceril palmitate and was mostly observed in VLBW infants.[54] The mechanism by which exogenous surfactants could cause pulmonary haemorrhage is not understood. It has been suggested that exogenous surfactants might increase left to right ductal shunt[55] and/or cause the intra-alveolar rupture of extremely frail lung capillaries in the more immature neonates,[56] or perhaps be directly cytotoxic.[57]

The use of exogenous surfactants has been associated with a decrease of other early lung complications of RDS, (e.g. the incidence of pneumothorax associated with RDS has decreased by 70%). The same seems true for other pulmonary

Table III. Meta-analysis of randomised controlled trials of prophylactic treatment with exogenous surfactant (reproduced from Soll,[53] with permission)

Major complications of prematurity	No. of trials	Odds ratio for natural surfactant extracts (95% CI)	No. of trials	Odds ratio for synthetic surfactants (95% CI)
Pneumothorax	8	0.31 (0.22-0.44)[a]	5	0.64 (0.45-0.89)[a]
Bronchopulmonary dysplasia (day 28)	7	0.88 (0.67-1.15)	5	1.09 (0.80-1.47)
Bronchopulmonary dysplasia or death (day 28)	7	0.64 (0.49-0.84)[a]	3	0.82 (0.63-1.08)
Patent ductus arteriosus	8	1.16 (0.89-1.50)	6	1.27 (1.03-1.57)[a]
Peri-intraventricular haemorrhage grade 1-4	8	0.95 (0.73-1.24)	4	0.94 (0.73-1.21)
Neonatal mortality	8	0.60 (0.42-0.85)[a]	7	0.67 (0.52-0.88)[a]

a Significant difference at 5% or less.

Abbreviation: CI = confidence interval.

Table IV. Meta-analysis of randomised controlled trials of rescue treatment with exogenous surfactant (reproduced from Soll,[53] with permission)

Major complications of prematurity	No. of trials	Odds ratio for natural surfactant extracts (95% CI)	No. of trials	Odds ratio for synthetic surfactant (95% CI)
Pneumothorax	12	0.34 (0.27-0.44)[a]	4	0.52 (0.42-0.65)[a]
Bronchopulmonary dysplasia (day 28)	10	1.01 (0.81-1.27)	3	0.68 (0.46-0.99)[a]
Bronchopulmonary dysplasia or death (day 28)	10	0.66 (0.53-0.82)[a]	3	0.56 (0.45-0.71)[a]
Patent ductus arteriosus	12	0.96 (0.79-1.18)	3	0.73 (0.60-1.88)
Peri-intraventricular haemorrhage grade 1-4	10	0.94 (0.76-1.15)	2	0.77 (0.62-0.97)[a]
Neonatal mortality	11	0.59 (0.47-0.74)[a]	5	0.65 (0.50-0.82)[a]

a Significant difference at 5% or less.

Abbreviation: CI = confidence interval.

leak events such as interstitial emphysema, although their occurrence is less accurately reported.

Unfortunately, the meta-analysis[53] revealed that the early benefits of exogenous surfactants did not extend to a later decrease of the overall incidence of pulmonary sequelae, i.e. bronchopulmonary dysplasia (BPD) usually defined at 28 postnatal days by supplemental oxygen requirement and typical lung changes on the chest x-rays. The meta-analysis[53] suggested that the overall BPD incidence was significantly reduced (by 30%) only in neonates receiving the rescue strategy using synthetic surfactants. However, a closer look at 3 peer-reviewed studies[6,58,59] revealed that the decrease in BPD incidence was significant only in infants with a birthweight of ≥1250g, and the BPD rate in the control group was very low (3%), indicating that the study population was at very low risk of BPD.[6] A literature based meta-analysis[60] of 27 trials with BPD as outcome, but restricted to those infants who were still alive at 28 postnatal days, showed that exogenous surfactants resulted in a significantly reduced rate of BPD in survivors, and a significantly lowered combined incidence of BPD and mortality, except in prophylactic trials with synthetic surfactants. In addition, it seemed that BPD severity was decreased by use of exogenous surfactants.[6,59] The true impact of exogenous surfactants on BPD rates might be buffered by their beneficial effects in terms of increased survival of the more immature low birthweight infants, in which the evolution towards BPD depends more on the immature lung development than on the severity or even presence of neonatal lung disease.

4.2 Patent Ductus Arteriosus

A meta-analysis[53] has suggested that natural surfactant extracts do not change the incidence of patent ductus arteriosus (PDA). However, the meta-analysis also showed that prophylaxis with synthetic surfactants appears to increase the incidence of PDA, while rescue treatment appears to decrease it; however, this may reflect more the design differences of the trials included in the meta-analysis than a true clinical fact. A detailed analysis of trials showed that systemic/pulmonary circulatory changes might represent more the clinical expression of the left to right ductal shunt than the PDA incidence itself.[61]

4.3 Perinatal Brain

A meta-analysis[53] has shown that natural surfactant extracts do not significantly modify the overall incidence of peri-intraventricular haemorrhages (PIVH), although separate prophylactic/rescue trials have demonstrated a reduced incidence.[9,10] A unique trial[62] showed an increase in major PIVH (grade III-IV). However, this result was not confirmed by a reanalysis of all the controlled randomised studies carried out with the same natural surfactant extract (beractant).[63] The reanalysis did reveal a slight increase in minor

PIVH (grade I-II) in the more immature neonates weighing 600 to 750g. An increased rate of minor PIVH was also reported in a subgroup of infants who had presented with hyperoxia (oxygen >30 kPa) at 30 minutes after the instillation of natural porcine surfactant extract. This risk, therefore, demands the most punctilious avoidance of hyperoxia after instillation.[9,10,29] Meta-analyses[53] of clinical trials of colfosceril palmitate have acknowledged a slightly diminished incidence of PIVH (all grades) but only when it is used in the rescue strategy and only for the more mature babies (with a birthweight of >1250g, as for BPD).[6] The decreases in PIVH incidence reported in 2 studies using the synthetic surfactant pumactant are difficult to analyse because PIVH ultrasound grading was either not standardised among centres in 1 study,[8] or not available in all centres in the other one.[64]

The paucity of data related to periventricular leucomalacia precluded a valid evaluation of the relationship between surfactant therapy and this complication.

4.4 Survival

Finally, the most striking benefit of the efficacy of exogenous surfactant has been the significant improvement in survival (by about 40%) in treated infants, whatever their gestational age and birthweights (though in various degrees). This effect of surfactants is thought to be the cause of the reduction of infant mortality seen in the US from 9.7/1000 births in 1989 to 9.1/1000 births in 1990.[65] To date, the neonatal mortality of babies with RDS has stabilised at around 20%.[66,67]

4.5 Other Outcomes

The impact of exogenous surfactants upon the incidence and severity of retinopathy of prematurity (ROP) was recently re-evaluated. Though the overall incidence has remained unchanged, it seems that the use of exogenous surfactants has reduced the rate of severe forms of ROP (stages 3 to 4), which are associated with a detrimental functional outcome.[68,69]

A small number of unsatisfactory adverse effects have been described in association with surfactant use: an increase in apnoea with colfosceril palmitate[52] and an increase in nosocomial infections[5] and necrotising enterocolitis[70] with beractant. Such unexpected findings reflect more the heterogeneity of neonatal intensive care than a specific effect of exogenous surfactants.

4.6 Long Term Outcomes

A number of survivors from controlled randomised studies for surfactants in RDS have now been followed up; data of their performance at 1 to 2 years of age are available, although the reliability of these data is highly variable both in terms of sources and methods of neuro-developmental evaluation. However, it is possible to cautiously draw a few general conclusions.[71-76]

The growth (height and bodyweight) of surfactant-treated infants is similar to the growth of control infants not treated with surfactants. The respiratory outcome of surfactant-treated infants is at least as good as that seen in controls. Two studies have reported a decrease in respiratory morbidity (rate of wheezing, recurrent respiratory infections, allergic respiratory symptoms) reflecting the reduced severity of BPD after exogenous surfactant.[71,75] Four series of functional explorations were carried out at 1 to 2.5 years of age: all showed similar lung volumes, compliance, resistance in treated and control children.[77-80] Two series reported a better total lung resistance in treated children versus controls.[77,78]

The sensory and neurodevelopmental outcome was not significantly modified at 1 and 2 years of age in treated infants. But these early comforting results need to be confirmed in children more than 3 years of age and hopefully at the time of primary school. To date, encouraging but scanty data have appeared for 5 to 7-year-old children, but most of it has been published in the form of abstracts.[81]

4.7 Extremely Premature Infants

Extremely premature neonates, with a gestational age of <26 weeks or a birthweight of <750g,

have usually not been included in randomised controlled trials of exogenous surfactants. Yet 2 trials (1 prophylactic and 1 rescue trial) have investigated this very premature population, using colfosceril palmitate.[82,83] Both trials showed that, in spite of a clear efficacy of surfactants on gas exchange, as well as a reduced incidence of pneumothorax in the prophylactic trial, this surfactant did not reduce the mortality nor the morbidity of these neonates. The 1 year outcome of survivors did not show any significant difference in treated versus control infants in either trial.[68,84]

Data from trials of natural surfactant extracts are at variance. A unique retrospective analysis showed that prophylaxis with beractant increased the survival rate of treated neonates with a gestational age of between 23 to 26 weeks in comparison with a control group, but the neurodevelopmental outcome at 23 months of age was the same in both groups.[85] Therefore the short and long term efficacy of exogenous surfactants is far from being proven in this range of prematurity in which survival is associated with an unfavourable neurodevelopmental outcome in half the cases.

5. Potential Risks

The sources and manufacturing procedures of exogenous surfactants carry potential risks which must be taken into account in an assessment of the risks and benefits of surfactant therapy.

5.1 Contamination with Infective Organisms

Consideration of the direct bacterial or viral infectious risks associated with exogenous surfactants is warranted because of the nature of the origin and selection of donor animals and the extraction techniques that involve organic solvents and sterilising procedures. The possible transmission of small proteinaceous infectious particles (prions) from surfactants has also been questioned. This is no small matter in Europe for bovine surfactant extracts because of the discovery in 1986 of an epizootic, bovine spongiform encephalitis (BSE). However, the cattle used for surfactant extraction are selected from BSE-free countries. There is no such concern for PLS, since no prion disease has been found in the swine family.

5.2 Inflammatory Risks

The theoretical risk that instillation of exogenous surfactants might induce some inflammatory lung reaction has been studied, with varying results. Natural and synthetic surfactants have, indeed, potent *in vitro* anti-inflammatory properties[86,87] but their *in vivo* effects are divergent. A few studies have reported a reduced activation of phagocytes[88] while others have suggested an increased inflammatory reaction, or at least a stimulation of acute phase proteins production (C-reactive protein, elastase-α_1-proteinase inhibitor complex).[88-90] Instillation of exogenous surfactant might then limit the reliability of specific protein levels to diagnose neonatal infection. Additional studies are required to understand the mechanism(s) and possible consequences of such changes.

5.3 Immunogenicity of Surfactant Preparations

It is now widely accepted that specific proteins as well as surfactant phospholipids are antigenic with a cross-reactivity between human/bovine/porcine surfactant extracts.[91,92] During RDS, some leakage of endogenous/exogenous surfactant components occurs and it may thus induce a humoral and/or cellular immune reaction.

A weak humoral reaction has been observed with enzyme-linked immunosorbent assay (ELISA) methods, such as immune complexes or free antibodies in the serum of premature neonates after treatment or no treatment by natural human/bovine/porcine surfactants.[73,93,94] However, results were not uniform.[73,93-97] If heterologous specific proteins of exogenous natural surfactant extracts are antigenic then they do not appear to trigger a stronger immune reaction in premature neonates than autologous specific proteins do. A few reports even showed a protective effect of natural surfactant extracts against an early immuno-

globulin (Ig) M reaction.[94] We are not aware of any similar studies with synthetic surfactants.

As far as cellular reactions are concerned, the results obtained with natural surfactant extracts do not support an increased lymphocyte proliferation.[97,98]

Finally, if the antigenicity of exogenous surfactants remains a fundamental topic, it is noteworthy that, to date, no deleterious clinical consequences have been reported. However, the ELISA measured level of SP-A/antiSP-A immune complexes has been significantly associated with the evolution towards BPD in neonates treated or not treated by a human natural surfactant extract.[99]

5.4 Inhalation of Platelet Activating Factor

The phospholipid mediator PAF is synthesised in fetal and adult type II pneumocytes and is secreted into the alveolus as part of the lamellar bodies. Natural surfactant extracts contain significant amounts of PAF.[99,100] In theory, inhalation of PAF by surfactant instillation might induce some bronchoconstriction, an increase in pulmonary vascular resistance and pulmonary oedema (by activating leukotrienes). No such harmful effects have been reported, either in clinical trials or in pharmacodynamic animal studies.

6. Optimal Strategies for Surfactant Replacement Therapy

6.1 Timing of Treatment

The very first experiments by Enhörning and Robertson[101] conducted in 1972 in premature rabbits suggested that the prophylactic use of exogenous surfactants, that is use before the first breath, was more effective than use after a short period of spontaneous breathing or mechanical ventilation. Most other experimental models of RDS have confirmed this observation.[102] However, in clinical practice much controversy still surrounds the relative advantages and disadvantages of surfactant prophylaxis (table V). Two meta-analyses,[103] (H. Walti, et al., unpublished observations) of 6 randomised trials comparing prophylactic versus rescue strategies with natural surfactant extracts, analysed data from more than 2700 neonates (gestational age of 25 to 32 weeks) and made several findings (table VI). [104-109] In all trials but one, the RDS severity (gas exchange and/or ventilatory support) was lessened with the prophylactic strategy. This result was associated with a significant decrease in neonatal and total mortality rate, and in pneumothorax and pulmonary emphysema incidence. The incidence of PIVH (grades I-IV) and of BPD in survivors also decreased with the prophylactic strategy, but not significantly. In addition, the meta-analysis of individual data from 3 trials involving PLS (671 infants) showed that the prophylactic strategy was associated with a significant decrease in the incidence of severe RDS, the rate of BPD in survivors and the incidence of PIVH (especially severe PIVH, grades III-IV).[110,111]

In spite of the better efficiency of the prophylactic strategy, there is still controversy regarding the benefit/risk ratio of prophylaxis and its excessive economic cost. However, using prophylaxis rather than rescue therapy would be expected to prevent 1 death for every 14 babies treated. Furthermore, to date, no trial has directly compared the prophylactic use to very early rescue treatment (therapy given within 2 hours of birth). But 2 trials have shown that early replacement using either

Table V. Potential advantages and disadvantages of prophylactic surfactant replacement therapy

Potential advantages	Potential disadvantages
Facilitates initial lung aeration and resorption of lung liquid	Implies the treatment of surfactant-sufficient premature infants (about 40% of infants with a gestational age of <31 wks)
Improves distribution of administered surfactant	Could destabilise the postnatal adaption phase
Decreases lung baro/volotrauma and prevents leakage of inhibitory serum proteins	Exposes surfactant-sufficient premature infants to: i) unnecessary endotracheal intubation and mechanical ventilation ii) unnecessary exposure to the theoretical adverse effects of exogenous surfactant iii) unnecessary costs
	Cannot be applied universally

Table VI. Meta-analysis of randomised controlled trials of prophylactic versus rescue treatment with natural surfactant extracts (Walti et al., unpublished observations)

Major complications of prematurity	No. of trials	No. of patients with the complication/total no. for prophylaxis (%)	No. of patients with the complication/total no. for rescue (%)	Odds ratio (95% CI)	No. needed to treat to obtain an effect
Pneumothorax	6[104-109]	42/1265 (3.3)	68/1250 (5.4)	0.59 (0.39-0.90)[a]	48
Pulmonary interstitial emphysema	5[104,106-109]	32/103 (3.1)	52/1006 (5.2)	0.55 (0.33-0.89)	48
Bronchopulmonary dysplasia in survivor (day 28)	6[104-109]	217/1182 (18.4)	226/1112 (20.3)	0.84 (0.67-1.06)	
Patent ductus arteriosus	6[104-109]	344/1269 (27.1)	354/1251 (28.3)	0.95 (0.79-1.13)	
Peri-intraventricular haemorrhage grade 1-4	6[104-109]	338/1214 (27.8)	365/1201 (30.4)	0.85 (0.70-1.03)	
Peri-intraventricular haemorrhage grade 3-4	6[104-109]	100/1214 (8.2)	118/1201 (30.4)	0.82 (0.61-1.10)	
Neonatal mortality (day 28)	6[104-109]	87/1269 (6.9)	139/1251 (11.1)	0.55 (0.41-0.75)[a]	24
Total mortality	4[104-106,108]	66/506 (13.0)	101/498 (20.3)	0.59 (0.42-0.82)[a]	14

a Significant difference at 5% or less.

Abbreviation: CI = confidence interval.

PLS or colfosceril palmitate achieved better results than delayed therapy.[67,112]

6.2 Optimal Dosage

The pool of endogenous alveolar surfactant amounts to at least 100 mg/kg in full term newborns, but it is usually less than 10 mg/kg in premature babies with RDS. Replacement therapy must therefore provide a minimum of 90 mg/kg of exogenous surfactant. A greater quantity may be required in case of lesion oedema (inactivation by plasma proteins).

The dose-dependency of the immediate efficacy of some exogenous surfactants has been well documented. A randomised study with PLS showed that an initial dose of 200 mg/kg improved gas exchange more rapidly than a 100 mg/kg dose, but the mid term results were unchanged.[66] Similar results were obtained with beractant.[113]

Repeat administration (as routine or against relapsing RDS) has been required to achieve sufficient efficacy of some surfactants (beractant and colfosceril palmitate)[5,67] or it has enhanced the efficacy of others over a single dose [PLS and calf lung surfactant extract (CLSE)].[114,115]

The dosage of PLS that produces optimal efficacy, regardless of the treatment strategy used, is 240 mg/kg; higher doses (e.g. 600 mg/kg) have not been associated with any better effect.[66] For colfosceril palmitate, a dosage of 135 mg/kg in 2 doses is optimal (4 doses produced had no better results).[52]

6.3 Natural Surfactant Extracts versus Colfosceril Palmitate

The debate over whether natural surfactant extracts or colfosceril palmitate is superior has been resolved largely by direct comparator studies involving large groups of patients. To date, animal experiments as well as pharmacodynamic studies have demonstrated the superior immediate effectiveness of natural surfactant extracts on respiratory function.[116] Table VII summarises the more recent meta-analysis[117] of 7 clinical directly comparative trials using natural surfactant extracts (6 with beractant,[23,118-122] 1 with CLSE[22]) versus the synthetic surfactant colfosceril palmitate in the treatment of established RDS.

Data showed that natural surfactant extracts achieved a more pronounced immediate decrease in oxygen requirement and ventilatory support (a benefit extending up to 72 hours after treatment).

The meta-analysis supports the theory that the natural surfactant extracts significantly reduce the

risk of pneumothorax. A trend towards decreased mortality and combined incidence of death and bronchopulmonary dysplasia was noted. No disadvantages were noted in association with natural surfactant extracts therapy.[117]

The only trial comparing a natural surfactant extract (CLSE) to colfosceril palmitate in the prophylaxis of RDS suggests also that CLSE is a more effective exogenous surfactant than colfosceril palmitate in reducing the incidence and the severity of RDS, the incidence of pulmonary air leaks and the mortality attributable to RDS. However, the use of CLSE was also associated with a greater risk of overall (grade 1 to 4) but not severe (grade 3 to 4) PIVH.[123]

In conclusion, although both natural surfactant extracts and colfosceril palmitate are effective in the treatment of established RDS, there is a trend in favour of the preferential use of natural surfactant extracts.

6.4 Comparing Natural Surfactant Extracts

Biophysical characteristics and experimental *in vivo* efficacy of the various natural surfactant extracts employed in routine practice are different.[24] Differences are probably linked with the biochemical composition of surfactants which is influenced by the origin of the extract and its preparation (see table I). The relevance of SP-B protein concentration has been stressed.[124,125] Two randomised trials compared the clinical efficacy of natural surfactant extracts. They involved PLS versus beractant (as rescue therapy) or CLSE versus beractant (as prophylactic and rescue therapy).[126,127] Both studies showed that PLS and CLSE had a greater efficacy than beractant in improving gas exchange and reducing ventilatory support during the 24 to 48 hours following randomisation. The difference was significant only for the rescue trials and was not associated with decreased use of surfactant. No difference was found in mortality/morbidity rates, but the sample size (around 100) was too small for a clearcut conclusion.

7. Economic Impact of Surfactant Replacement Therapy

The immediate cost of surfactant therapy (US$1000 to US$2000) is small in comparison

Table VII. Meta-analysis of randomised controlled trials of natural surfactant extracts versus synthetic surfactant colfosceril palmitate (Exosurf® Neonatal™) in treatment of established respiratory distress syndrome (reproduced from Soll,[117] with permission)

Major complications of prematurity	Natural surfactant extracts (number of trials)[a]	No. of patients with the complication/total no. for natural surfactants (%)	No. of patients with the complication/total no. for synthetic surfactants (%)	Typical relative risk (95% CI)	No. needed to treat to obtain an effect
Pneumothorax	Beractant (3)[23,118,119] CLSE (1)[22]	141/1539 (9.2)	205/1527 (13.4)	0.69 (0.57-0.85)[b]	24
Bronchopulmonary dysplasia (day 28)	Beractant (4)[23,118-120]	451/1110 (40.6)	504/1212 (41.6)	0.96 (0.87-1.06)	
Bronchopulmonary dysplasia or death (day 28)	Beractant (2)[23,119]	540/958 (56.4)	571/952 (60.0)	0.94 (0.87-1.01)	28
Patent ductus arteriosus	Beractant (4)[23,118-120]	482/1109 (43.5)	578/1209 (47.8)	0.94 (0.86-1.03)	
Peri-intraventricular haemorrhage grade 1-4	Beractant (3)[23,119,120]	372/1000 (37.2)	379/1086 (34.9)	1.05 (0.94-1.18)	
Peri-intraventricular haemorrhage grade 3-4	Beractant (3)[23,118,119]	150/962 (15.6)	148/954 (15.5)	1.01 (0.82-1.24)	
Total mortality	Beractant (6)[23,118-122] CLSE (1)[22]	258/1687 (15.3)	303/1774 (17.1)	0.87 (0.75-1.01)	58

a Number of trials with each type of natural surfactant versus colfosceril palmitate included in the meta-analysis.

b Significant difference at 5% or less.

Abbreviations: CI = confidence interval; CLSE = calf lung surfactant extracts.

with the total hospital cost for neonatal intensive care. It is now established that costs per survivor are reduced after surfactant therapy, especially in larger infants.[128-132] This saving (of about $10 000 per survivor) reflects the lower cost for ancillary services (such as radiology and laboratory tests) and are the direct consequences of the efficacy of surfactant therapy. However, this cost saving could be offset by the additional cost caused by the increased number of survivors still at risk for unfavourable and costly neurodevelopmental outcome.[133] Nonetheless, the costs per quality-adjusted life year (QALY) for survival in surfactant-treated infants are low when compared to the costs per QALY of other medical or surgical interventions in adults.[130,134]

8. Conclusion

The mid and long term benefit : risk ratio is in favour of the use of exogenous surfactants to prevent or to treat RDS in neonates with a gestational age of >26 weeks or a birthweight of >750g. The results of randomised trials are confirmed by open studies which report routine use.[132,135-137] Some open studies achieved better results than randomised trials, which may be explained by a learning curve[138] and/or the introduction of more systematic use of prenatal glucocorticoids that have been shown to have synergistic effects towards surfactants.[139]

However, the optimal strategy of administration of surfactant therapy remains debated. Indeed, although practical observations seem to favour the superiority of prophylactic use of natural surfactant extracts, many neonatologists are still reluctant to give 'needless' treatment to 1 neonate out of 2. Furthermore, even in the absence of comparative data, the possible economic extra cost of prophylaxis scares institutions and often curbs the preferential use of prophylaxis in spite of its saving 1 extra baby per 14 treated neonates. A similar controversy restrains the preferential use of natural surfactant extracts in spite of their being superior and innocuous agents compared with synthetic surfactants.

To date, responses to these areas of controversy rely only on each neonatologist's personal practice and institutional constraints, when the time comes to prescribe expensive surfactants to prevent or to treat RDS.

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