The choice of surfactant for treatment of respiratory distress syndrome in preterm infants: A review of the evidence

There are many clinical trials of surfactant therapy in newborn babies, but making valid comparisons between surfactant preparations is problematic due to the different doses, volumes and treatment schedules used. This article reviews the evidence available from clinical trials comparing different surfactant preparations and describes a meta-analysis of three randomised, controlled trials comparing Curosurf and Survanta.

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Keywords

surfactant; respiratory distress syndrome; Curosurf; Survanta

Key points

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1. Natural surfactants have important advantages over currently available synthetic surfactants.
2. Curosurf has short term and possibly some long term benefits over Survanta.
3. Results of clinical trials of 'new generation' synthetic surfactants are awaited.

Fujiwara first described the use of surfactant replacement therapy for neonatal respiratory distress syndrome (RDS) in 1980[1]. This was followed by a large number of randomised, controlled trials in which many thousands of babies have been studied. The resulting widespread use of surfactant replacement therapy has revolutionised the initial respiratory management of preterm infants, and is undeniably one of the major advances in neonatal intensive care.

Since Fujiwara's initial publication, a wide variety of surfactant preparations have been studied, some synthetically produced and others derived from animal sources. This review will present the evidence currently available from comparative studies of various surfactant preparations.

Synthetic or animal surfactant?

Human surfactant consists of dipalmitoyl phosphatidylcholine (DPPC), other lipids including unsaturated phosphatidylcholine, phosphatidylglycerol, phosphatidylinositol and neutral lipids, as well as the surfactant associated proteins SP-A, SP-B, SP-C and SP-D. These make up approximately 10% of the total mass and have various functions, which enhance surfactant function.

Surfactants produced commercially may be from animal (natural) or synthetic sources. The main structural difference between natural or animal derived surfactants and those produced synthetically is the inclusion in the former of surfactant associated proteins SP-B and SP-C in concentrations of 1-2%. It has been suggested that this produces the greater efficacy of natural surfactants demonstrated in animal models[2].

	RR	95% CI for RR	NNT
Pneumothorax	0.63	0.53 - 0.75	23
PDA	0.98	0.91 - 1.06	-
PIVH	1.09	1.00 - 1.19	36
Severe PIVH (grades 3/4)	1.08	0.92 – 1.28	-
ROP	0.95	0.88 - 1.01	-
CLD (28 days)	1.02	0.93 - 1.11	-
CLD (36 weeks)	1.01	0.90 - 1.12	-
Mortality	0.86	0.76 – 0.98	37
Mortality or CLD (28d)	0.95	0.90 – 1.01	-
Mortality or CLD (36w)	0.98	0.90 – 1.06	40

TABLE 1 Meta-analyses of natural versus synthetic surfactant from Soll and Blanco 2001[6].

Both natural and synthetic surfactants have been shown to be effective in reducing mortality and pulmonary air leak (pneumothorax and PIE), when used prophylactically in preterm neonates at risk of RDS[3,4] (**FIGURE 1**). Prophylactic synthetic surfactant is associated with an increased risk of pulmonary haemorrhage. Synthetic surfactant has been shown to reduce the risk of mortality, pulmonary air leak, patent ductus arteriosus (PDA), peri-intraventricular haemorrhage (PIVH) and chronic lung disease (CLD) in preterm infants with established RDS[5].

Eleven randomised, controlled trials have been published to date, comparing natural and synthetic surfactants in preterm infants at risk for or having RDS. Meta-analyses of the results of these trials showed reduced mortality and pneumo-

thorax associated with natural surfactant use. This was also associated with a marginal increase in the risk of PIVH, but no increase in severe (grade 3 or 4) PIVH. No significant differences were noted for other outcomes, including CLD (**TABLE 1**)[6].

The apparent advantages of the currently available natural surfactants over synthetic preparations available up until now have led to widespread preference for natural surfactant use over the past few years. Prior to this, synthetic surfactants were promoted as being cheaper, of more uniform composition, with no theoretical risk of transmission of infective diseases (such as New Variant Creuzfeld Jacob Disease) and no possible risk of sensitisation to animal proteins.

A new generation of synthetic surfactants is currently under evaluation. These consist of phospholipids combined with synthetic peptides, which mimic the repeating stretches of hydrophobic residues with intermittent basic hydrophilic residues seen in SP-B. Results of animal studies and phase 1 clinical trials of one such preparation, KL4-surfactant, have been promising, and publication of randomised, controlled trials comparing this to natural surfactants are currently awaited[7,8].

Which natural surfactant?

A number of different natural surfactant preparations have been assessed in clinical trials over the past 20 years. These differ in their animal of origin, composition, appearance, availability, recommended dosage and cost (**TABLE 2**). There are marked differences between the various preparations for concentration of phospholipid (ranging from 25 to 80mg/mL), dose (ranging from 50 to 200mg/kg) and volume of each dose (ranging from 1.2mL/kg to 5mL/kg).

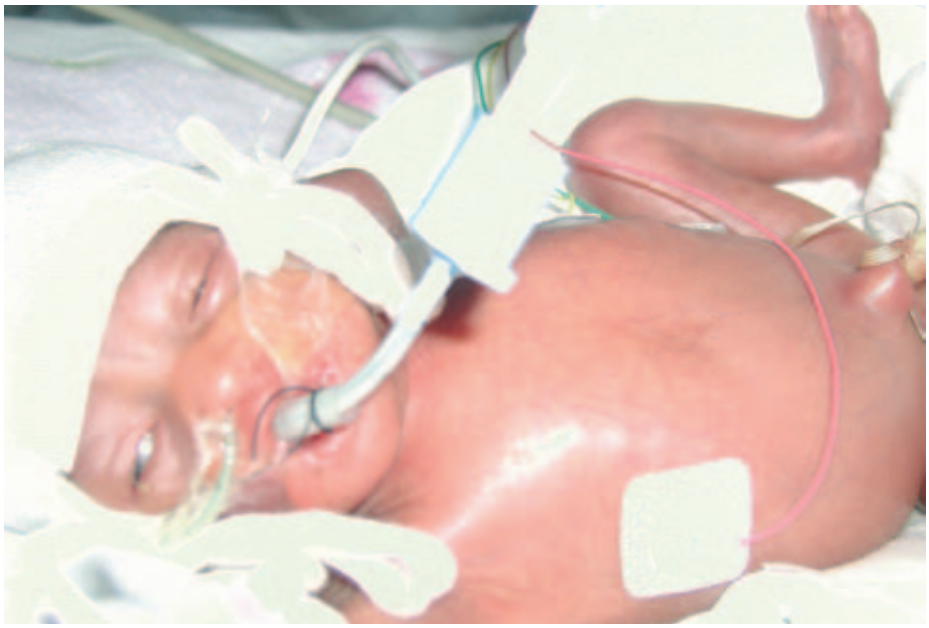

FIGURE 1 Surfactant being administered to a 26 week gestation infant.

A number of animal studies have suggested that the physiological effect of different natural surfactant preparations may be influenced by their composition[9-11].

Clinical trials comparing different natural surfactant preparations

Clark et al carried out a retrospective study of outcomes of 5169 preterm neonates in 114 neonatal units who had been treated with either Calfactant (Infasurf) or Beractant (Survanta). A stepwise logistic regression analysis suggested that there were no differences in mortality or other outcomes associated with the type of surfactant preparation used[12].

To date, only four randomised, controlled trials have compared the efficacy of different natural surfactant preparations, assessing Beractant (Survanta), Calfactant (Infasurf), Poractant (Curosurf) and Bovactant (Alveofact). **TABLE 3** shows details of trial design for each of these.

Speer et al compared Curosurf to Survanta in a pilot study, with a number of short-term end-points defined for oxygenation or ventilator settings[13]. Although the initial dose of Curosurf was twice that of Survanta (200mg/kg versus 100mg/kg), the maximum total dose was 400mg/kg for each arm of the trial, if repeat dosing was required. Both groups showed a quick and favourable response in terms of oxygenation and reduction in ventilatory support, but infants randomised to receive Curosurf had statistically significant higher arterial:alveolar oxygen tension ratios (a/A) and lower peak inspiratory and mean

Generic name	Trade name	Composition	Surfactant protein content	Phospholipid concentration	Dose	Volume	Availability in UK
Beractant	Survanta® (Ross, USA)	Bovine, minced lung + DPPC, trimalmitin & palmitic acid	<0.5% SP-B & C	25mg/mL	100mg/kg	4mL/kg	Yes
Bovine Lipid Extract Surfactant	BLES® (BLES Biochemicals, Canada)	Bovine lung lavage	~1% SP-B & C	27mg/mL	135mg/kg	5mL/kg	No
Bovactant	Alveofact® (Thomae, Germany)	Bovine lung lavage	~1% SP-B & C	41.7mg/mL	50mg/kg	1.2mL/kg	No
Calfactant	Infasurf® (ONY Inc., USA)	Bovine lung lavage	SP-B 290g/mL SP-C 360g/mL	33.3mg/mL	100mg/kg	3mL/kg	No
Poractant alfa	Curosurf® (Chiesi, Italy)	Porcine minced lung	~1% SP-B & C	80mg/mL	100-200mg/kg	1.25-2.5mL/kg	Yes
Surfactant TA	Surfacten® (Tokyo Tanabe, Japan)	Bovine, minced lung + DPPC, trimalmitin & palmitic acid	<0.5% SP-B & C	30mg/mL	120mg/kg	4mL/kg	No

TABLE 2 Natural surfactant preparations used in clinical trials.

	Inclusion criteria	Surfactants (& dose)	No. randomised	
Speer et al 1995[13]	BW 700-1500g RDS, ventilated, FiO_2 ≥0.4, 1-24 hours age	**Curosurf 200mg/kg** or **Survanta 100mg/kg** (repeat doses up to max. total dose 400mg/kg for each surfactant)	Curosurf Survanta Total	33 40 73
Bloom et al 1997[14]	Treatment arm – BW <2000g RDS, ventilated, FiO_2 ≥0.4, PaO_2 <80Torr or a/A ≤0.22 Prevention arm – BW <1250g, <30 wks. gestation, <15 mins. age	**Infasurf 100mg/kg** or **Survanta 100mg/kg** (up to 3 repeat doses 100mg/kg each)	Treatment arm – Infasurf Survanta Total Prevention arm – Infasurf Survanta Total	 303 305 608 180 194 374
Baroutis et al 2003[15]	BW ≤2000g, ≤32 wks. gestation, RDS, ventilated, FiO_2 ≥0.3, <4 hours age	**Alveofact 100mg/kg** or **Curosurf 100mg/kg** or **Survanta 100mg/kg** (2nd dose 12 hours after 1st in all babies & up to 2 further doses if required)	Alveofact Curosurf Survanta Total	27 27 26 80
Ramanathan et al 2004[16]	BW 750-1750g, <35 wks, RDS, ventilated, FiO_2 ≥0.3 to maintain O_2 sat. 88-96% or a/A ≤0.3, <6 hours age	**Curosurf 100mg/kg** or **Curosurf 200mg/kg** or **Survanta 100mg/kg** (up to 3 repeat doses 100mg/kg if required)	Curosurf 100mg/kg Curosurf 200mg/kg Survanta Total	96 99 98 293

TABLE 3 Details of RCT's comparing natural surfactants.

	Survanta n/N (%)	Curosurf n/N (%)	RR	95% CI
Pulmonary haemorrhage	6/133 (5%)	12/228 (5%)	0.98	0.38 – 2.54
Air leak	18/164 (11%)	15/255 (6%)	1.54	0.78 – 3.06
PDA	62/164 (38%)	102/255 (40%)	0.98	0.77 – 1.25
PIVH 3/4	14/138 (10%)	18/228 (8%)	0.98	0.65 – 2.68
CLD (36 weeks)	41/156 (26%)	74/240 (31%)	0.99	0.72 – 1.35
>1 dose	73/138 (53%)	84/228 (37%)	1.36	1.08 – 1.72
Mortality	21/156 (13%)	18/240 (8%)	1.71	0.93 – 3.14

TABLE 4 Meta-analyses of Survanta versus Curosurf.

airway pressures at several points within the first 24 hours. There was also a lower incidence of complications associated with Curosurf administration (0% versus 12.5%; P=0.057), and the need for more than two doses was lower in this group (40.0% versus 18.2%; P=0.07). There was a trend towards better clinical outcomes in the Curosurf group, with lower mortality and incidence of pneumothorax and severe PIVH, although these differences failed to reach statistical significance, possibly due to the relatively small sample size.

Bloom et al compared identical doses of Infasurf and Surfactant in a large number of babies who were treated either prophylactically or as treatment for established RDS[14]. Babies randomised to receive Infasurf in both the prophylaxis and treatment parts of the study, had longer intervals between doses, suggesting an increased duration of treatment effect with Infasurf. Significantly more babies receiving Survanta in the treatment part of the study required four or more doses. Infasurf was associated with better oxygenation and lower mean airway pressure during the first 48 hours for those in the treatment part of the study. There was a statistically significant increase in mortality in babies with birthweight less than 600g, randomised to receive Survanta in the prevention part of the study. However, numbers were small (6/23 (26%) versus 19/30 (63%); P=0.007), and this could therefore represent a type 1 error. No other differences were found for clinical outcomes[14].

In 2003, Baroutis et al reported their study results comparing identical doses (100mg/kg) of Alveofact, Curosurf and Survanta for established RDS[15]. The study was blinded with regards to Alveofact and Curosurf, but not Survanta due to the volume and different method of administration. Babies randomised to receive Alveofact and Curosurf spent fewer days on the ventilator and in supplemental oxygen and had a shorter hospital stay when compared with those receiving Survanta. There were no statistically significant differences for other clinical outcomes. As well as the lack of blinding and the relatively small sample size, this study was limited due to the relatively high mean birthweight (1195g, 1233g and 1180g for Alveofact, Curosurf and Survanta respectively) and high mean gestational age (29.0, 28.7 and 29.2 weeks).

Recently Ramanathan et al published the findings of their randomised, controlled trial comparing Curosurf and Survanta[16]. Preterm infants were randomised to one of three groups, receiving an initial dose of either Curosurf (100mg/kg), Curosurf (200mg/kg) or Survanta (100mg/kg). Short term changes in oxygen requirements were compared by assessing the fraction of inspired oxygen (FiO_2) between 0 and 6 hours, by measuring the area under the curve (FiO_2 AUC_{0-6}). Babies in both the Curosurf groups had significantly lower oxygen requirements compared to those who received Survanta. In addition, the Curosurf 200mg/kg group needed less repeat doses of surfactant, and showed

reduced mortality up to 36 weeks post-conceptional age in infants born ≤ 32 weeks gestation. All other outcomes were similar for all the three groups, including the incidence of pneumothorax, pulmonary haemorrhage, PDA, necrotising enterocolitis (NEC), PIVH grade 3/4 and CLD.

Meta-analyses of clinical trials comparing different natural surfactants

Three of the four published randomised, controlled trials of different natural surfactants have compared Curosurf to Survanta[13,15,16]. These are the only two licensed surfactant preparations currently available in the United Kingdom. Using meta-analysis it is possible to combine the results of these trials in order to estimate any possible differences between the two preparations with greater certainty. **TABLE 4** summarises the results of these meta-analyses.

There is a greater risk of requiring more than one dose of Survanta compared to Curosurf (**FIGURE 2**). In numerical terms, for approximately every six babies treated with Curosurf rather than Survanta, one baby would avoid the need for retreating.

There is also a strong trend towards a reduced risk of mortality with Curosurf compared to Survanta (**FIGURE 3**) and a trend towards a reduced risk of air leak favouring Curosurf (**FIGURE 4**).

Although two different doses of Curosurf (100mg/kg and 200mg/kg) have been used in the trials included in these meta-analyses, the maximum total dose given was the same, and also equal to the maximum total dose of Survanta. Also, the initial recommended dose of Curosurf is 100-200mg/kg and it is common practice to give smaller babies a higher dose (up to 200mg/kg) and larger babies a minimum of 100mg/kg of Curosurf, so that each opened vial is fully used (personal communication). The dose of Curosurf usually given to babies of various weights is shown in **TABLE 5**.

There are also three further limitations of the evidence available from these randomised, controlled trials and meta-analyses of their results. Firstly, the gestational ages and birthweights of babies studied in all four trials were relatively high (mean gestation ≥29 weeks; mean birthweight ≥1150g), thus excluding those at greatest risk of adverse outcome. There is therefore limited information regarding the best choice of natural surfactant for extremely preterm babies with birth-weights less than 1000g. Secondly, in three of the four trials, surfactant was only given to those with established RDS and not prophylactically. Mean age at the time of the first surfactant dose was 2.5-3 hours in two of the trials. Current evidence-based practice is to use surfactant prophylactically (i.e. as early as possible after birth) in babies at risk of RDS, in order to reduce the risk of mortality and lung injury[17]. Thirdly, none of the trials describe either long term respiratory or neurodevelopmental outcomes.

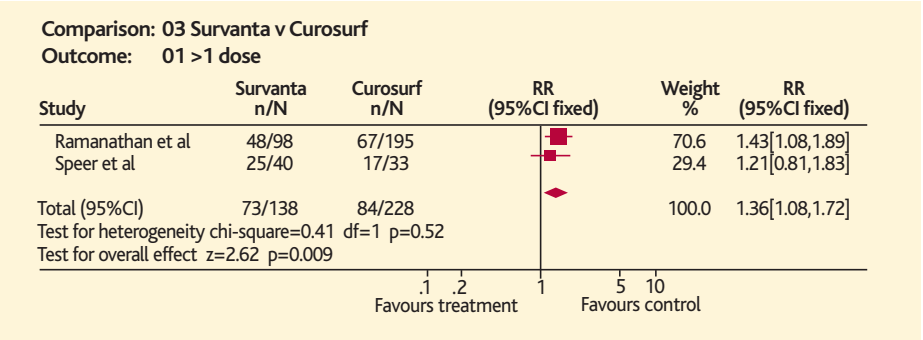

FIGURE 2 Metaview graph showing results of meta-analysis of Survanta v Curosurf for babies requiring >1 dose.

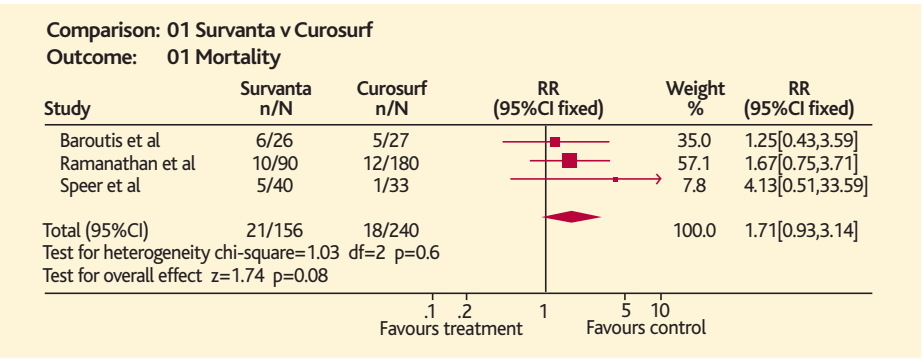

FIGURE 3 Metaview graph showing results of meta-analysis of Survanta v Curosurf for mortality.

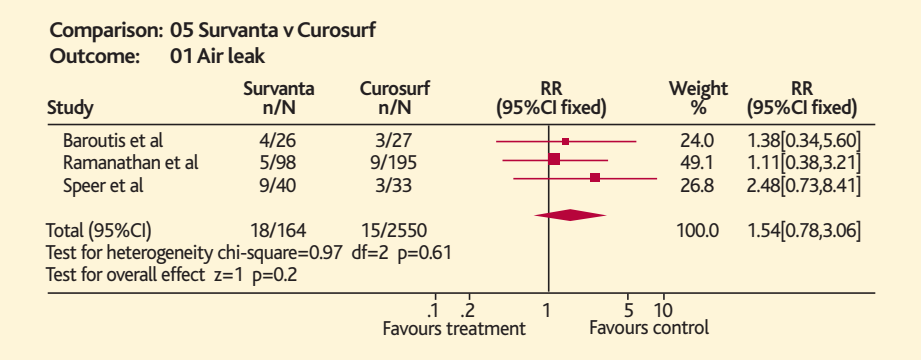

FIGURE 4 Metaview graph showing results of meta-analysis of Survanta v Curosurf for air leak.

Summary

Use of natural surfactants rather than the 'first generation' synthetic surfactants available until recently, leads to a reduced risk of mortality and lung injury in preterm infants with RDS.

Results of randomised, controlled trials of different preparations of natural surfactants suggest that Curosurf reduces the need for repeat dosing, is associated with fewer complications of administration, leads to better short-term oxygenation and may reduce the risk of mortality compared to Survanta. It is uncertain whether these apparent differences would also exist in extremely preterm infants, less than 27 weeks gestation and less than 800g birthweight, who are given their initial dose of surfactant prophylactically as soon as possible after birth. Information regarding long term outcomes is also lacking. These questions may remain unanswered, as further randomised, controlled trials comparing different natural surfactants are

Birth weight (g)	Dose given (120mg (1.5mL) /vial, max 1 vial per dose)
500	200mg/kg (1.25mL)
600	200mg/kg (1.5mL)
700	171mg/kg (1.5mL)
800	150mg/kg (1.5mL)
900	133mg/kg (1.5mL)
1000	120mg/kg (1.5mL)
1200	100mg/kg (1.5mL)

TABLE 5 Dose of Curosurf commonly used according to birthweight.

unlikely to be carried out due to the current development of a new generation of synthetic surfactants.

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