

CURRENT TOPIC

Surfactant treatment for premature babies— a review of clinical trials

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In the late 1950s it was shown that respiratory distress syndrome was associated with a deficiency of pulmonary surfactant.¹ In the last 10 years several different preparations of surfactant have now been the subject of randomised controlled trials.

Surfactants

Surfactant TA, developed in Japan (Tokyo-Tanabe), is extracted from homogenised cow lungs.²⁻⁶ To achieve optimum physical properties, dipalmitoylphosphatidylcholine, palmitic acid, and triglyceride are added. It contains 48% dipalmitoylphosphatidylcholine, 16% unsaturated phosphatidylcholine, 4% phosphatidylglycerol, 4% triglyceride, 8% fatty acids, 7% cholesterol, sphingomyelin, and other lipids and 1% apoproteins SpB and SpC. It is freeze dried and when used 100–200 mg is sonicated for five minutes with 3–4 ml saline.

The Japanese surfactant, modified by Abbott laboratories, is called *Survanta*.⁷⁻⁹ It is a frozen aqueous suspension of 25 mg/ml and contains approximately 88–90% phospholipids (of which 50% is disaturated phosphatidylcholine), 3% triglycerides, 6% free fatty acids, 1% protein, and 0.2% cholesterol. It is thawed before use in a dose of 4 ml/kg.

Calf lung surfactant (CLSE) is made by extracting surfactant from calf lungs.¹⁰⁻¹³ It contains 90–97% phospholipid of which 85% is phosphatidylcholine (70% disaturated), 6% phosphatidylglycerol, 4% phosphatidylinositol, 3% phosphatidylethanolamine, 1% sphingomyelin, and 5% cholesterol and cholesterol esters, and 1% protein which is mainly low molecular weight apoproteins SpB and SpC. It is sterilised by flash autoclaving. Before use 90 mg are vortexed with 3 ml of saline.

Porcine surfactant (Curosurf, Chiesi) is extracted from minced pig lungs.¹⁴⁻¹⁶ It consists of 99% lipids and 1% hydrophobic proteins with a molecular weight less than 15 kDa. It is used as a suspension of 80 mg/ml at 200 mg/kg.

Bovine surfactant (SF-R1 1; renamed Alveofact, Thomae) is extracted from cow lung lavage, containing 99% phospholipids and neutral lipids and 1% surfactant associated, proteins SpB and SpC.¹⁷ It is used in a suspension of 45 mg/ml.

Human surfactant is extracted from amniotic fluid.¹⁸⁻²⁰ It contains apoproteins SpA, SpB,

and SpC. It is used as 60 mg/kg suspended saline.

In Belfast an artificial surfactant was made from dipalmitoylphosphatidylcholine (1 g), high density lipoprotein (4 ml), and saline, sterilised by irradiation, sonicated just before use, and given as a 3–5 ml dose into the endotracheal tube at birth.²¹ This is no longer used.

Artificial lung expanding compound (ALEC, Pumactant, Britannia Pharmaceuticals) is made from dipalmitoylphosphatidylcholine and unsaturated phosphatidylglycerol in a w:w ratio of 7:3 and contains no protein.²²⁻³⁰ It has been used as a powder and as a suspension of 50 to 100 mg in 1 ml cold saline.

Exosurf (Wellcome) contains dipalmitoylphosphatidylcholine 108 mg, tyloxapol 8 mg, and hexadecanol 12 mg in 10 ml saline without protein.³¹ It is used as 5 ml/kg instilled into the endotracheal tube. Although preliminary results have been presented, there are no published reports of clinical trials.

Clinical trials

There are now at least 15 peer reviewed papers of controlled clinical trials. There are eight trials of surfactant given at birth called 'prophylactic treatment' and seven trials of surfactant given when babies with respiratory distress syndrome required ventilation, called 'rescue treatment'. The basic data about the trials are shown in tables 1 and 2.

Comparing the prophylactic and rescue trials is not satisfactory. Not least because the rescue trials enrol only seriously ill babies and the prophylactic trials include all babies at risk of developing respiratory distress syndrome. Comparisons between trials within prophylactic or rescue groups are difficult because the entry criteria were different. For example, in the prophylactic trials, some randomised all babies born below 35 weeks' gestation, and others enrolled only babies between 25 and 29 weeks' gestation. Some trials retrospectively excluded babies who had mature lecithin:sphingomyelin ratios; others included babies regardless of their lung maturity. In the rescue trials some enrolled babies receiving at least 60% oxygen, and others enrolled babies receiving more than 40% oxygen. Some trials entered all babies even if they were compromised by asphyxia, haemorrhage, infection, or very prolonged rupture of

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Table 1 Basic data for the prophylactic trials

| Author | Surfactant | Dose (mg) | Volume (ml) | Placebo | Control (n) | Surfactant (n) | Inclusion criteria (weeks' gestation) | Exclusion criteria | Retreatment |
|---------------------------------------|------------|-----------|-------------|---------|-------------|----------------|---------------------------------------|--|-------------|
| Enhörning <i>et al</i> ¹⁰ | CLSE | 75-100 | 3-4 | None | 33 | 39 | <30 | Acute deliveries | No |
| Kendig <i>et al</i> ¹³ | CLSE | 90 | 3 | Saline | 31 | 34 | 25-29 | Non-intubated babies | No |
| Kwong <i>et al</i> ¹¹ | CLSE | 90 | 3 | Saline | 13 | 14 | 24-28 | Congenital malformations, steroids | No |
| Merritt <i>et al</i> ¹⁹ | Human | 60 | 3 | Air | 29 | 31 | 24-29 | Congenital malformations, L:S>1.9, PG-ve | Yes |
| Halliday <i>et al</i> ²¹ | DPPC/HDL | 30 | 3-5 | None | 51 | 49 | 25-33 | Congenital malformations, L:S>1.9 | No |
| Morley <i>et al</i> ^{24, 25} | ALEC | 25 | Powder | None | 75 | 54 | <34 | Congenital malformations | No |
| Morley <i>et al</i> ^{25, 26} | ALEC | 50-100 | 1 | Saline | 171 | 170 | 23-34 | Congenital malformations | Yes |
| Ten centre ²⁷ | ALEC | 100 | 1 | Saline | 149 | 159 | 25-29 | Congenital malformations, not resuscitated | Yes |

CLSE, calf lung surfactant; DPPC/HDL, dipalmitoylphosphatidylcholine/high density lipoprotein; ALEC, artificial lung expanding compound; L:S, lecithin:sphingomyelin; PG-ve, phosphatidylglycerol negative.

Table 2 Basic data for the rescue trials

| Author | Surfactant | Dose (mg/kg) | Volume (ml/kg) | Placebo | Control (n) | Surfactant (n) | Birth weight (g) | Inclusion criteria | Time (hours) |
|------------------------------------|---------------|--------------|----------------|---------|-------------|----------------|------------------|--|--------------|
| Hallman <i>et al</i> ¹⁸ | Human | 60 | 3 | None | 23 | 22 | <1500 | O ₂ >60%, MAP=8-10, low L:S, PG-ve, no sepsis | <10 |
| Lang <i>et al</i> ²⁰ | Human | 70 | 3 | None | 28 | 31 | <1500 | O ₂ >80%, PIP>18, no sepsis, air leak, or hydrops | <12 |
| Gitlin <i>et al</i> ² | Surfactant TA | 100 | 3.3 | Saline | 23 | 18 | 1000-1500 | O ₂ >40%, IPPV | <8 |
| Raju <i>et al</i> ⁶ | Surfactant TA | 100 | 3.3 | Saline | 13 | 17 | 751-1750 | O ₂ >50%, MAP=>8 | <6 |
| Collaborative ¹⁶ | Curosurf | 200 | 2.5 | None | 77 | 69 | 700-2000 | O ₂ >60%, IPPV, no complicating disease | 2-15 |
| Horbar <i>et al</i> ⁷ | Survanta | 100 | 4 | Air | 81 | 78 | 750-1750 | O ₂ >40%, IPPV, no fits, air leak sepsis, blood pressure normal | 3-6 |
| Horbar <i>et al</i> ⁸ | Survanta | 100 | 4 | Air | 53 | 53 | 750-1750 | O ₂ >40%, IPPV, no fits, air leak sepsis, blood pressure normal | 3-6 |

O₂, oxygen; MAP, mean airway pressure; PIP, peak inspiratory pressure; IPPV, intermittent positive pressure ventilation; all pressures in cm H₂O. L:S, lecithin:sphingomyelin; PG-ve, phosphatidylglycerol negative.

the membranes, whereas others excluded such babies, and one trial retrospectively excluded babies thought not to have respiratory distress syndrome. Many trials did not have sufficient numbers to take account of important variations factors such as birth weight, sex, mode of delivery, and antenatal factors. The European Curosurf trial showed that the response and effect on mortality was considerably influenced by non-randomised factors such as inspired oxygen concentration, age, birth weight, sex, and hospital where the baby was treated.¹⁶

The dose of surfactant used varied from 25 mg to 200 mg and the number of doses has varied from one to four. The criteria for retreatment also varied. Some trials stipulated retreatment by time others by whether or not the baby was intubated, and others by ventilator pressure level or inspired oxygen requirements. The surfactants were used in varying states from powder to sonicated or suspended solutions. The volumes vary from 1 to 8 ml. Some trials used no placebo for the controls, others used air or equal volumes of saline. Most trials have tried to 'blind' the neonatal unit staff from whether the baby received surfactant or was a control, others gave the surfactant openly. For these reasons,

comparison of the different surfactant preparations and trials cannot be precise.

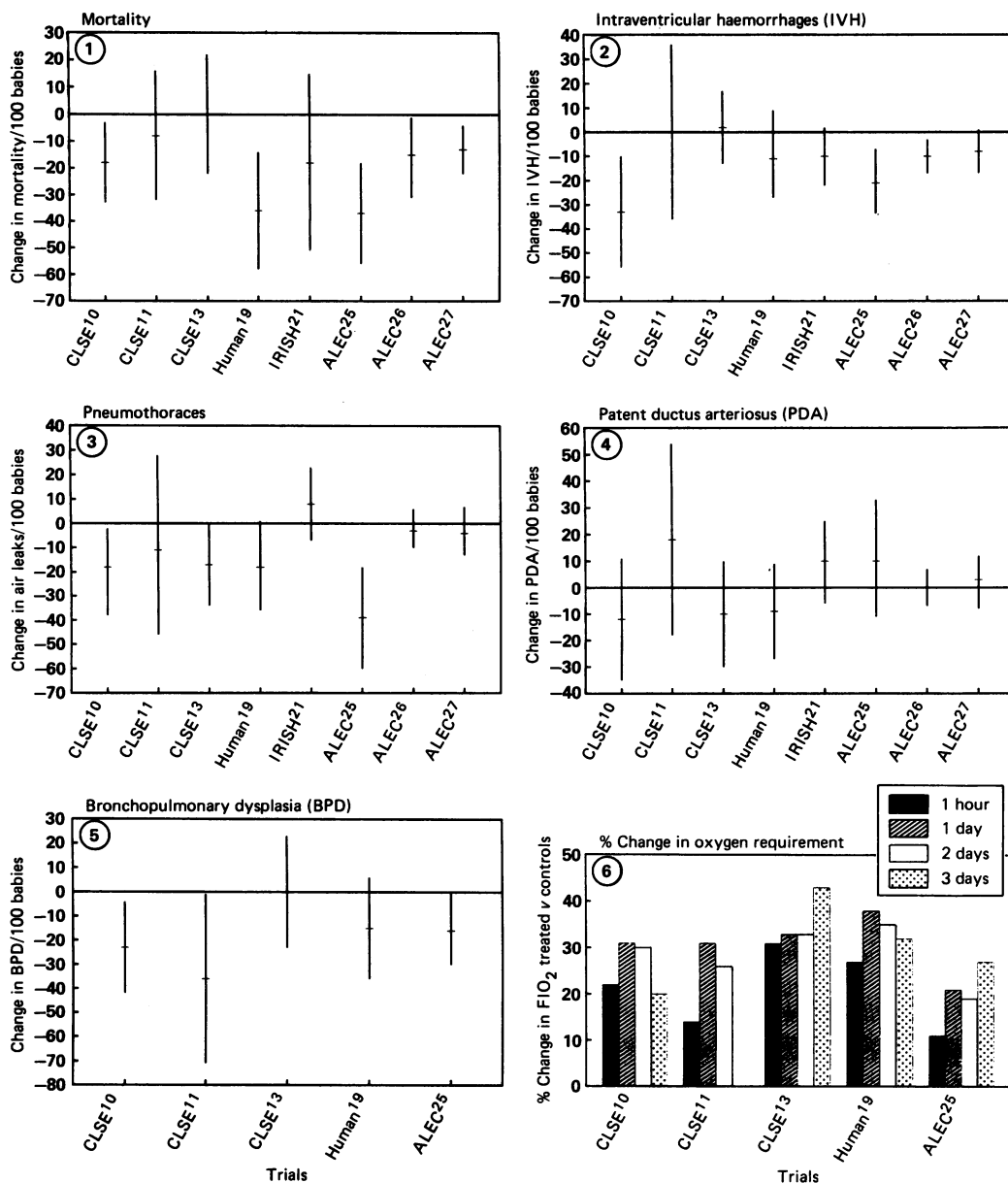
Outcome of the trials

Different outcomes have been stressed by different trials. Some have emphasised an improvement in oxygenation whereas others have used a reduction in mortality, bronchopulmonary dysplasia, or periventricular haemorrhage. There are no published data on the trials of Exosurf, although unpublished data suggest it has beneficial effects.

The major outcomes are shown in the figures as 95% confidence intervals for the difference in incidence between the treated and control groups. Only the trials accurately reporting the data are included.

MORTALITY

Mortality is a crude but important measure of surfactant treatment. Where possible this has been calculated for babies under 30 weeks' gestation. No surfactant treatment has been reported to increase the mortality. It is shown in fig 1 for the prophylactic trials and fig 7 for the



Figures 1-6 Prophylactic trials. Bars are 95% confidence intervals for difference in incidence between treated and control groups. CLSE, calf lung surfactant; ALEC, artificial lung expanding compound.

rescue trials. In the rescue trials confidence intervals are wide because of small numbers. Only the trial of Raju *et al* of surfactant TA⁶ and the trial of Curosurf¹⁶ demonstrated significant reductions in mortality. In the prophylactic trials, there were significant reductions in mortality with one trial of CLSE,¹⁰ but not in the other two, human surfactant,¹⁹ ALEC powder,²⁵ and ALEC suspension.^{26 27} Overall surfactant treatment approximately halved the mortality. This might be spuriously high because some trials were stopped when a significant difference in mortality was noted.

It should be appreciated that in those trials where surfactant reduced mortality there were more surfactant treated babies surviving to be at risk of other complications.

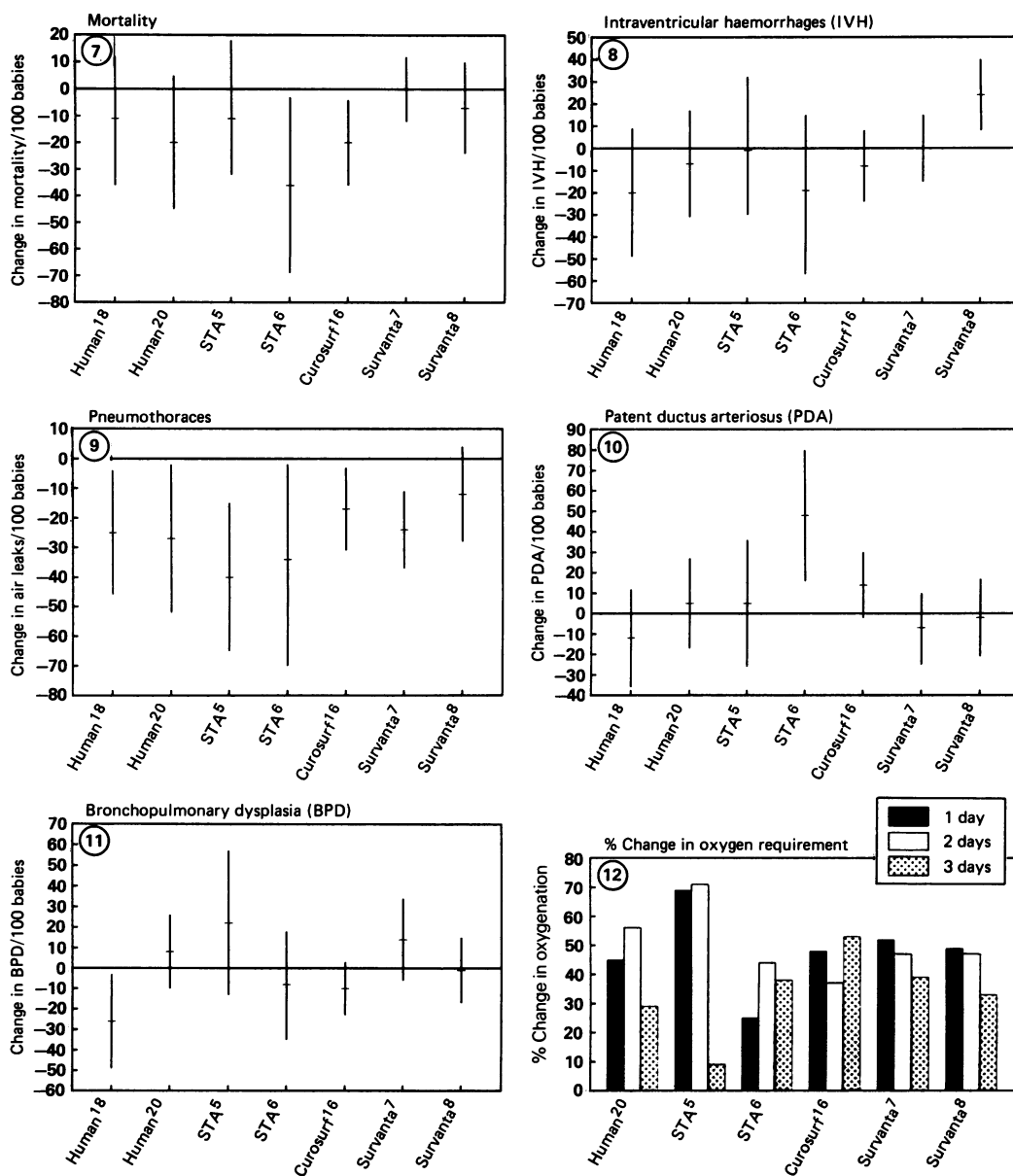
INTRAVENTRICULAR HAEMORRHAGE

Figures 2 and 8 show the effect of different surfactants on intraventricular haemorrhage. If

trials reported the percentage of babies with grade 3 or 4 haemorrhages these are presented otherwise the numbers represent the total number of intraventricular haemorrhages. Although the trial of McCord *et al* with Curosurf¹⁵ showed a significant reduction this was a subgroup from the European Curosurf trial,¹⁶ which showed no effect on intraventricular haemorrhage, even grade 3 and 4. Survanta showed no effect in the American trial⁷ but a significant increase in the European trial.⁸ In the prophylactic trials, significant reductions in brain haemorrhages were shown by one trial of CLSE,¹⁰ ALEC suspension in the Cambridge-Nottingham trial,²⁶ and ALEC powder.²⁵

PNEUMOTHORAX

The effect of the different trials is shown in figs 3 and 9. As surfactant lowers surface tension it was originally thought that its clinical use might lead to overdistension of the lungs and increase



Figures 7–12 Rescue trials. Bars are 95% confidence intervals for difference in incidence between treated and control groups. STA, Surfactant TA.

the incidence of pneumothoraces. The rescue trials all produced a reduction in pneumothoraces that were significant except for the European trial of Survanta.⁸ The prophylactic trials showed a significant reduction in the incidence of pneumothoraces in only two of the trials of CLSE^{10 13} and one trial of ALEC powder.²⁵

PATENT DUCTUS ARTERIOSUS

In the first non-randomised trial of Fujiwara *et al* patent ductus arteriosus occurred in nine out of 10 babies and it looked as though this may be a major side effect of surfactant treatment.² Figures 4 and 10 show the incidence of patent ductus arteriosus. In the rescue trials surfactant treatment tended to increase the incidence of patent ductus arteriosus, although this effect was only significant in one trial of Surfactant TA.⁶ The trial of Curosurf had a 57% increase in the babies requiring surgical closure or indomethacin treatment in the surfactant

treated group.¹⁶ In the prophylactic trials none had a significant effect on the incidence. No trial showed a significant reduction in patent ductus arteriosus.

BRONCHOPULMONARY DYSPLASIA

The incidence of bronchopulmonary dysplasia is not reported in all trials. Figures 5 and 11 show that surfactant treatment has a variable effect on the incidence. In the rescue trials only human surfactant showed a significant reduction in one trial.¹⁸ In the prophylactic trials only CLSE^{10 11} and ALEC²⁵ showed a significant reduction.

CHANGES IN OXYGENATION

All trials have shown a reduction in the oxygen requirements. Figures 6 and 12 show the effect of different surfactant preparations on oxygenation over the first three days, presented as the

percentage improvement caused by the surfactant treatment. Although surfactant treatment improves oxygenation the effect is only demonstrable in most of the trials during the first few days with little effect over seven days. All rescue trials show a significant reduction in oxygen requirement. In the five prophylactic trials where this data is presented there is also a reduction in oxygen requirements.

TIME IN OXYGEN AND RECEIVING VENTILATION

With more survivors surfactant treatment could result in babies receiving respiratory support for a longer time. Not all the trials give the length of time babies received oxygen. In the trial of Gitlin *et al* of Surfactant TA there was a significant reduction in time receiving oxygen but not in the time to extubation.⁵ Whereas in the trial of Raju *et al* with Surfactant TA there were no significant differences.⁶ In the trial of Curosurf there was no significant difference in the duration of artificial ventilation.¹⁶ In the 10 centre trial of ALEC there was a significant reduction in the hours of ventilation and hours in more than 30% oxygen for survivors at 10 days. In the high dose/low dose randomised trial of Surfactant TA significantly fewer of the babies receiving the high dose were ventilated for 30 days or more.³

CHANGES IN AIRWAY PRESSURE

Not all trials show changes in ventilator pressure. They have shown a consistent improvement during the first three days with a reduction in mean airway pressure of between 2 and 5 cm H₂O. Taking account of the numbers of babies and severity of disease in the different trials there is no significant difference in the effect of different surfactants.

CHANGES IN COMPLIANCE OF THE RESPIRATORY SYSTEM

Both natural surfactant and artificial surfactants can improve thoracic compliance of premature animals.^{30 31} ALEC improves the compliance of the respiratory system in babies less than 30 weeks' gestation from 0.54 to 0.91 ml/cm H₂O/kg ($p < 0.05$) by six hours after prophylactic treatment.²⁹ This is not apparent in babies of 30 weeks or more. Couser *et al* in a prophylactic trial of Survanta measured dynamic compliance during ventilation in unparalysed babies.⁹ They showed no difference in the lung compliance, resistance, or tidal volume at one hour after each dose compared with the controls. However, the compliance of the surfactant treated group increased over seven days. In the first 72 hours the compliance of the controls was approximately 0.35 ml/cm H₂O/kg and the surfactant treated approximately 0.55 ml/cm H₂O/kg. By day seven, the controls had a compliance of 0.45 ml/cm H₂O/kg and the surfactant treated 0.85 ml/cm H₂O/kg ($p < 0.05$).

VARIATION IN INDIVIDUAL RESPONSE

Despite early beliefs that all babies with respiratory distress syndrome were surfactant deficient

and therefore surfactant treatment would cure them, not all babies respond to treatment. Fujiwara and others have reported that with Surfactant TA approximately two thirds had an immediate and sustained response in oxygenation, one sixth relapsed, and one sixth had a poor or no response.^{32 33} They thought that the factors leading to an unsatisfactory response were a patent ductus arteriosus, cardiogenic shock or persistent fetal circulation, and air leaks. It is not surprising that these very immature babies, who suffer from so many compounding diseases and complications, should not always respond to surfactant treatment. Perhaps it is more surprising that so many do.

FOLLOW UP

Few follow up studies have been reported. In a group of 235 Cambridge born survivors from a randomised trial of ALEC follow up information was available for 98% at 18 months.³⁴ There was no difference between ALEC treated and control babies in the incidence of neurological impairment, mental impairment, respiratory infections, allergies, or hospital admissions up to 18 months' post-term. In those born before 30 weeks' gestation (where surfactant most improves survival) the proportion of normal survivors was 57% in the treated group compared with 41% of the controls. Similar results have been reported for other surfactants by Vaucher *et al*³⁵ and Halliday *et al*.³⁶ Improved neonatal survival does not appear to be associated with neurodevelopmental handicap.

Conclusion

The overview of all the trials of surfactant treatment shows that it benefits babies less than 30 weeks' gestation. The only major side effect is in the rescue trials where there was an increase in patent ductus arteriosus in babies treated with natural surfactant.

Prophylactic treatment is beneficial and apparently harmless, even though some babies who would not have developed respiratory distress syndrome were treated.

One of the concerns about natural surfactant preparations is the protein to which babies may become sensitised. The evidence to date is that any antibodies which are produced do not appear to cause problems.

Although it has been suggested that artificial surfactant is not as effective as natural surfactant because it does not contain the apoproteins,³⁷ the results of the trials of artificial surfactant ALEC have shown that it reduces the incidence of neonatal complications and improves the outcome of babies less than 30 weeks' gestation at least as well as natural surfactants.

The evidence suggests that the surfactants most likely to have longer term benefits are CLSE, human surfactant, and ALEC when used prophylactically and Curosurf used in rescue mode. The decision about which surfactant should be used will depend upon its possible side effects, its ease of preparation and delivery, its availability, and its price.

- 1 Avery ME, Mead J. Surface properties in relation to atelectasis and hyaline membrane disease. *Am J Dis Child* 1959;97:517-23.
- 2 Fujiwara T, Chida S, Watabe Y, Maeta H, Morita T, Abe T. Artificial surfactant therapy in hyaline membrane disease. *Lancet* 1980;i:55-9.
- 3 Konishi M, Fujiwara T, Takeuki Y, et al. Surfactant replacement therapy in neonatal respiratory distress syndrome. *Eur J Pediatr* 1988;144:20-5.
- 4 Tanaka Y, Takei T, Kanazawa Y, et al. Preparation of surfactant from minced bovine lung, chemical composition and surface tension properties. *Journal of the Japanese Medical Society of Biological Interface* 1982;13:27-34.
- 5 Gitlin JD, Soll RF, Parad RB, et al. Randomized controlled trial of exogenous surfactant for the treatment of hyaline membrane disease. *Pediatrics* 1987;79:31-7.
- 6 Raju TNK, Vidyasagar D, Bhat R, et al. Double-blind controlled trial of single-dose treatment with bovine surfactant in severe hyaline membrane disease. *Lancet* 1987;i:651-6.
- 7 Horbar JD, Soll RF, Sutherland JM, et al. A multicentre, randomized, placebo controlled trial of surfactant therapy for respiratory distress syndrome. *N Engl J Med* 1989;320:959-65.
- 8 Horbar JD, Soll RF, Schachinger H, et al. A European multicenter randomized controlled trial of single dose surfactant therapy for idiopathic respiratory distress syndrome. *Eur J Pediatr* 1990;149:416-23.
- 9 Couser RJ, Ferrara B, Ebert J, Hoestra RE, Fangman JJ. Effects of exogenous surfactant therapy on dynamic compliance during mechanical breathing in preterm infants with hyaline membrane disease. *J Pediatr* 1990;116:119-24.
- 10 Enhorning G, Shennan A, Possmayr F, Dunn M, Chen CP, Milligan J. Prevention of neonatal respiratory distress syndrome by tracheal instillation of surfactant. A randomized clinical trial. *Pediatrics* 1985;76:145-53.
- 11 Kwong SM, Egan EA, Notter RH, Shapiro DL. Double-blind clinical trial of calf lung surfactant extract for the prevention of hyaline membrane disease in extremely premature infants. *Pediatrics* 1985;76:585-92.
- 12 Shapiro DL, Notter RH, Morin FC, et al. Double blind, randomized trial of calf lung surfactant extract administered at birth to very premature infants for prevention of respiratory distress syndrome. *Pediatrics* 1986;76:593-9.
- 13 Kendig J, Notter RH, Cox C, et al. Surfactant replacement therapy at birth: final analysis of a clinical trial and comparisons with similar trials. *Pediatrics* 1988;82:756-62.
- 14 Noack G, Berggren P, Curstedt T, et al. Severe neonatal respiratory distress syndrome treated with isolated phospholipid fraction of natural surfactant. *Acta Paediatr Scand* 1987;76:697-705.
- 15 McCord FB, Curstedt T, Halliday HL, et al. Surfactant treatment and the incidence of intraventricular haemorrhage in severe respiratory distress syndrome. *Arch Dis Child* 1988;63:10-6.
- 16 Collaborative multicenter study group. Surfactant replacement therapy for severe neonatal respiratory distress syndrome: an international randomized clinical trial. *Pediatrics* 1988;82:683-91.
- 17 Gortner L, Pohlandt F, Disse B, Weller E. Effects of bovine surfactant in premature lambs after intratracheal application. *Eur J Pediatr* 1990;149:280-3.
- 18 Hallman M, Merritt TA, Jarvenpaa AL, et al. Exogenous human surfactant for treatment of severe respiratory distress syndrome: a randomized prospective clinical trial. *J Pediatr* 1985;106:963-9.
- 19 Merritt TA, Hallman M, Bloom BT, et al. Prophylactic treatment of very premature infants with human surfactant. *N Engl J Med* 1986;315:785-90.
- 20 Lang MJ, Hall RT, Reddy NS, Kurth CG, Merritt TA. A controlled trial of human surfactant replacement therapy for severe respiratory distress syndrome in low birth weight infants. *J Pediatr* 1990;116:295-300.
- 21 Halliday HL, McClure G, Reid M, Lappin TRJ, Meban C, Thomas PS. Controlled trial of artificial surfactant to prevent respiratory distress syndrome. *Lancet* 1984;i:476-8.
- 22 Bangham AD, Morley CJ, Phillips MC. The physical properties of an effective lung surfactant. *Biochim Biophys Acta* 1979;573:552-6.
- 23 Bangham AD, Miller NGA, Davies RJ, Greenough A, Morley CJ. Introductory remarks about artificial lung expanding compound (ALEC). *Colloid and Surfaces* 1984;10:337-47.
- 24 Morley CJ, Bangham AD, Miller N, Davis JA. Dry artificial surfactant and its effect on very premature babies. *Lancet* 1981;i:64-8.
- 25 Morley CJ. The Cambridge experience of artificial surfactant. In: Walters DV, Strang LB, Geubelle F, eds. *Physiology of the fetal and neonatal lung*. Lancaster: MTP Press, 1987:255-72.
- 26 Morley CJ, Greenough A, Miller N, et al. Randomized trial of artificial surfactant (ALEC) given at birth to babies from 23 to 34 weeks gestation. *Early Hum Dev* 1988;17:41-54.
- 27 Ten Centre Study Group. Ten centre trial of artificial surfactant (ALEC) in very premature babies. *BMJ* 1987;294:991-6.
- 28 Wilkinson A, Jenkins PA, Jeffrey JA. Two controlled trials of dry artificial surfactant: early effects and later outcome in babies with surfactant deficiency. *Lancet* 1985;ii:287-91.
- 29 Morley CJ, Greenough A. Respiratory compliance in premature babies treated with artificial surfactant (ALEC). *Arch Dis Child* 1991;66:467-71.
- 30 Morley CJ, Robertson B, Lachmann B, et al. Artificial surfactant and natural surfactant. Comparative study of the effects on premature rabbit lungs. *Arch Dis Child* 1980;55:758-65.
- 31 Durand DJ, Clyman RI, Heymann MA, et al. Effects of a protein-free, synthetic surfactant on survival and pulmonary function in preterm lambs. *J Pediatr* 1985;107:775-80.
- 32 Fujiwara T, Konishi M, Chida S, Maeta H. Factors affecting the response to a postnatal single dose of a reconstituted bovine surfactant (Surfactant TA). In: Lachmann B, ed. *Surfactant replacement therapy*. Berlin: Springer Verlag, 1988:91-107.
- 33 Charon A, Taesch W, Fitzgibbon C, Smith G, Treves S, Phelps D. Factors associated with surfactant treatment response in infants with severe respiratory distress syndrome. *Pediatrics* 1989;83:348-54.
- 34 Morley CJ, Morley R. Follow up of premature babies treated with artificial surfactant (ALEC). *Arch Dis Child* 1990;65:667-9.
- 35 Vaucher YE, Merritt TA, Hallman M, et al. Neurodevelopment and respiratory outcome in early childhood after human surfactant treatment. *Am J Dis Child* 1988;142:927-30.
- 36 Halliday HL, McClure G, McReid M. Growth and development two years after artificial surfactant replacement at birth. *Early Hum Dev* 1986;13:323-7.
- 37 Shapiro DL. Development of surfactant replacement. In: Shapiro DL, Notter RH, eds. *Surfactant replacement therapy*. New York: Alan R Liss, 1989:1-17.