Respiratory compliance in premature babies treated with artificial surfactant (ALEC)

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Abstract

In a randomised trial of artificial surfactant (ALEC) given at birth to 294 babies less than 34 weeks' gestation, the respiratory compliance was measured at 1, 6, 24, 48, and 168 hours after birth. In babies less than 29 weeks' gestation ALEC significantly improved the mean (SEM) compliance at 6 hours from 0·54 (0·06) to 0·91 (0·13) ml/cm H_2O/kg and at 24 hours from 0·57 (0·04) to 0·92 (0·10) ml/cm H_2O/kg. The improvements at 1, 48, and 168 hours were not significant. In babies of over 29 weeks' gestation the compliance was lower in the ALEC treated babies. This was significant only at one hour: 0·52 (0·03) compared with 0·71 (0·07) ml/cm H_2O/kg and only occurred in babies who were not ventilated.

Several randomised trials have shown that surfactant treatment of premature babies improves their oxygenation and ventilation. Only one has reported the effect of surfactant treatment on pulmonary mechanics in non-randomised babies.[1]

This paper reports measurements of the respiratory compliance made during a randomised trial of artificial surfactant given at birth to babies under 35 weeks' gestation. The surfactant, called artificial lung expanding compound (ALEC, Pumactant, Britannia Pharmaceuticals) is a protein free mixture of two pure phospholipids. The formulation, properties, and details of the trials have been described.[2–4]

Experiments to assess the effect of ALEC on respiratory compliance in premature rabbits at 27 days' gestation showed that it significantly improved the compliance after one hour's ventilation from 0·07 to 0·27 ml/cm H_2O/kg (p<0·05) and after one hour's spontaneous breathing from 0·10 to 0·58 ml/cm H_2O/kg.[5]

When ALEC was given prophylactically to babies less than 30 weeks' gestation, it significantly reduced the inspired oxygen concentration and ventilator pressure requirements in the first few days. It also significantly reduced the time babies required artificial ventilation, the time they were treated with more than 30% oxygen, the mortality, and the incidence of intracerebral haemorrhage.[2 4 6]

Accurately measuring respiratory compliance in ill premature babies is difficult.[7] In a clinical trial where babies are studied at predetermined times it is not possible to control for many of the factors that influence respiratory compliance. The techniques used for measuring compliance in this study were applied to babies in both treated and control groups. Thus despite the problems with possible inaccuracy of individual measurements the statistical comparison of two large randomised groups should be valid.

Subjects and methods

TRIAL PROTOCOL

Unselected babies born in Cambridge between 23 and 34 weeks' gestation were entered into the trial and randomised from sealed envelopes just before delivery. Babies randomised to surfactant were treated with 50–100 mg of ALEC powder, mixed with 1 ml of saline at 4°C just before use, and controls received 1 ml of saline. At birth surfactant or saline was put into the pharynx. If the baby was intubated, further doses were given through the endotracheal tube at 10 minutes, 1 hour, and 24 hours. Randomisation and giving the designated treatment were undertaken by the research team and these were not disclosed to the clinical teams. Babies were excluded from the analysis if they were stillborn or had gross congenital malformations. The trial was analysed by treatment as randomised.[8] The protocol was approved by the Cambridge District Health Authority ethics committee.

Two hundred and ninety four babies were entered into the trial, of whom 13 (4%) were excluded. Table 1 shows the distribution of factors in the two groups, in which compliance was measured, which might influence the severity of lung disease and thus respiratory compliance.

MEASUREMENT OF RESPIRATORY COMPLIANCE

Compliance was measured, where possible, at 1, 6, 24, 48, and 168 hours. Babies were supine in their own incubator. Sleep state could not be recorded. Signals were recorded on a polygraph (Gould 2600) with a full scale frequency response of 60 Hz. The pressure transducers (Mercury) and their tubing had a 90% rise time of approximately 30 ms, confirmed by the balloon burst technique. They were calibrated daily against a water column.

Tidal gas flow was measured using a pneumotachograph (Mercury F10L) with a dead space of 1·8 ml, this was attached either to a close fitting face mask or between the endotracheal tube and the ventilator circuit. It was calibrated with a syringe. The response was linear up to 18 l/minute. The flow signal was electronically integrated (Gould integrator No 13-4615-70) to tidal volume.

Oesophageal pressure was measured using hand made latex balloons approximately 2 cm

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Table 1 Basic data for the two treatment groups

	All babies		Babies <30 weeks' gestation	
	Surfactant treated (n=102)	Controls (n=108)	Surfactant treated (n=48)	Controls (n=48)
Mean (SE) birth weight (g)	1441 (48)	1391 (44)	1089 (46)	1034 (38)
Mean (SE) gestational age (weeks)	29·6 (0·2)	29·7 (0·2)	27·4 (0·2)	27·4 (0·2)
No (%) males	24 (46)	55 (50)	24 (51)	29 (59)
No (%) PROM*	28 (27)	25 (23)	13 (28)	12 (24)
No (%) with pre-eclampsia	25 (25)	37 (34)	11 (23)	15 (31)
No (%) having caesarean section	57 (56)	62 (57)	23 (49)	29 (59)
No (%) going into labour	71 (70)	61 (56)	37 (79)	31 (63)
No (%) receiving antenatal:				
Steroids	7 (7)	7 (6)	5 (11)	4 (8)
β stimulants	28 (27)	25 (23)	19 (40)	16 (33)

*PROM, membrane ruptured for more than two days before delivery.

long, 0·5 cm wide, and 0·05 mm thick, on a size 6 French gauge neonatal feeding tube attached to a pressure transducer; a size 8 tube was considered to be too large for such small babies. The balloon was passed into the stomach and withdrawn into the oesophagus approximately 1 cm above the point where the baby's inspiration produced a negative deflection.[9][10] Ventilator pressure was measured from the nasotracheal tube (usually 3·0 mm) near the pneumotachograph.

The randomised treatment was given by the team who measured the compliance. This possible source of bias was overcome by coding the recordings and analysing them blind at a later date.

Respiratory compliance was related to birth weight but not to length because it is difficult to measure in small sick babies.

Compliance was calculated from the recordings of 10 breaths without artifacts.

Dynamic compliance

Dynamic compliance was calculated for those babies who were breathing spontaneously. In intubated babies tidal volume and oesophageal pressure were measured during a brief disconnection from the ventilator. The pressure difference for this calculation was taken from the airway pressure at points of zero air flow. Expiratory volumes were used for calculations of tidal volume to minimise any error from leakage around the uncuffed endotracheal tube. In nonintubated babies the pneumotachograph was attached to a closely fitting face mask and recordings of tidal volume and oesophageal pressure were made when the baby was quiet and the face mask leak free (the inspiratory and expiratory volumes were equal).

Static compliance

Static compliance measurements were only made when babies were apnoeic or paralysed with pancuronium. The respiratory compliance was calculated from the tidal volume and the applied ventilator pressure difference measured accurately from a recording of the waveform. Tidal volume was measured when the inflating pressure had been held for at least 0·5 seconds and the volume exchange had reached a plateau.

Reproducibility of compliance measurements

The reproducibility of both static and dynamic compliance was tested in 20 infants whose clinical condition remained stable over several hours (assessed by lack of change in blood gas values and ventilator settings). Compliance measurements were made at 0, 30, 60, 120, 180, and 360 minutes. The intrasubject coefficient of variation was 22·3% for static compliance and 30·3% for dynamic compliance. The apparent variability of the measurement may be explained by the relatively long period over which measurements were made. More frequent measurements in such fragile babies would have been inappropriate.

MISSING DATA

Of 1405 occasions when compliance should have been measured satisfactory recordings were obtained on 777. Measurements were not possible on the other occasions for a number of reasons: the equipment was faulty or being serviced (n=353), the research staff were unavailable (n=52), the baby had died (n=31), or had been transferred out of the unit (n=67). In addition, from baby 140 onwards no six hour measurements were made because of logistic difficulties with trying to make three recordings in 24 hours.

The number of compliance measurements for each treatment group are shown in table 2 as a

Table 2 Number of measurements made at each time and the percentage of the babies alive and eligible for the measurement

Time after birth (hours)	Surfactant treated		Controls	
	No eligible to be measured	No (%) measured	No eligible to be measured	No (%) measured
All babies:				
1	102	98 (96)	108	104 (96)
6	54	49 (91)	52	46 (84)
24	99	85 (86)	106	93 (88)
48	98	77 (79)	105	90 (86)
168	96	72 (75)	103	63 (61)
Babies less than 30 weeks' gestation:				
1	48	46 (96)	48	46 (96)
6	23	22 (96)	20	20 (100)
24	46	43 (93)	46	43 (93)
48	45	38 (84)	45	44 (98)
168	43	36 (84)	43	36 (84)

The number of babies eligible for each compliance measurement is the number of live babies in the study at each time, taking account of the times when measurements were not possible (see text). No six hour measurements were done after baby 139.

Table 3 Number (%) of babies who were ventilated in each group at each time

Time after birth (hours)	Surfactant treated	Controls
All babies:		
1	54/98 (55)	57/104 (55)
6	21/49 (43)	24/46 (52)
24	35/85 (41)	45/93 (48)
48	28/77 (36)	41/90 (45)
168	15/72 (21)	16/63 (25)
Babies less than 30 weeks' gestation:		
1	32/46 (70)	43/46 (93)
6	13/21 (62)	17/20 (85)
24	26/43 (60)	34/43 (79)
48	23/38 (61)	31/44 (70)
168	12/36 (33)	18/36 (50)

percentage of the babies who were alive and eligible for measurements at each time. Table 3 shows the number of ventilated babies measured at each time and their percentage of the recordings made. The proportions in the two groups are not significantly different.

Results

Table 4 shows the compliance for each group at each time. The results are divided into two groups: babies between 23 and 29 weeks' gestation and babies between 30 and 34 weeks' gestation. This division was made because most respiratory problems occur in babies under 30 weeks' gestation and the results were then comparable with most other trials of surfactant treatment who only entered babies under 30 weeks' gestation.[11-14] Student's *t* test was used to investigate statistically significant differences.

BABIES OF 23 TO 29 WEEKS' GESTATION

The profile of change in compliance was different in the ALEC treated and control groups. The compliance of the controls increased gradually over the first seven days, whereas the compliance of the surfactant treated babies rose rapidly in the first six hours and remained at a similar level for the next seven days with no significant change. The compliance was significantly greater in the surfactant treated babies at six and 24 hours.

BABIES OF 30 TO 34 WEEKS' GESTATION

The compliance increased in both groups over the first seven days. It was lower in the ALEC treated babies than in the controls. This was only significantly different at one hour. This difference was confined to the babies who were not ventilated (0·57 (0·05) compared with 0·82 (0·08)) whereas in the ventilated babies there was no difference (0·44 (0·04) compared with 0·40 (0·03)).

Discussion

Accurately measuring respiratory compliance in ill premature babies is difficult. In intubated babies air may leak around the endotracheal tube reducing the measured tidal volume. Spontaneous respiratory efforts during mechanical ventilation alter the inflation volume, rendering some static compliance measurements inaccurate.[15] In babies who are paralysed to assist ventilation static compliance measurements can easily be made but the chest wall component, although small, is altered by the loss of tone in the muscles. In intubated babies the resistance to gas flow in the endotracheal tube will alter the apparent respiratory compliance. The magnitude of this varies with each baby and is related to the internal diameter and length of the endotracheal tube. The end occlusion technique[16] is often invalidated in babies with respiratory distress syndrome because they actively expire during the obstruction.[15]

Spontaneously breathing babies with lung disease have retraction of the chest wall during inspiration[17]; this reduces the tidal volume for an inspiratory force. The magnitude of the retraction depends on the gestation, the severity of lung disease, the strength of the diaphragmatic contraction, the baby's position and sleep state. If dynamic compliance is measured during disconnection from the ventilator lung volume may fall because the larynx is bypassed by the endotracheal tube.

The validity of the dynamic compliance measurements also depends on accurately recording oesophageal pressure. Unfortunately, this measurement may be inaccurate because the oesophageal pressure in very premature babies varies from the cardiac sphincter to the thoracic inlet and accurate, consistent placement of the oesophageal balloon is difficult.[7] Traditional methods of assessing the accuracy of oesophageal pressure measurements are not possible or useful in ventilated infants.[9] Leaks around the endotracheal tube can prevent complete airway occlusion and where occlusion is possible it is

Table 4 Compliance measurements (ml/cm H₂O/kg) for each group at each time

Time after birth (hours)	Surfactant treated		Controls		p Value
	No of babies	Mean (SEM)	No of babies	Mean (SEM)	
Babies 23 to 29 weeks' gestation:					
1	46	0·60 (0·06)	46	0·53 (0·05)	NS
6	22	0·91 (0·13)	20	0·54 (0·06)	<0·05
24	43	0·92 (0·10)	43	0·57 (0·04)	<0·01
48	38	0·75 (0·09)	44	0·65 (0·08)	NS
168	36	1·03 (0·09)	36	0·89 (0·10)	NS
Babies 30 to 34 weeks' gestation:					
1	52	0·52 (0·03)	59	0·71 (0·07)	<0·05
6	29	0·56 (0·05)	28	0·72 (0·09)	NS
24	43	0·71 (0·07)	50	0·78 (0·07)	NS
48	41	0·73 (0·07)	47	0·88 (0·10)	NS
168	34	0·91 (0·08)	28	1·16 (0·11)	NS

very difficult to get the ratio of oesophageal and airway pressure close to unity because of the pressure gradient within the oesophagus.[7] [17] We have previously reported a good correlation in ventilated babies between pressure changes measured by the oesophageal balloon and those measured directly from a catheter draining a pneumothorax.[10] Although this confirms the ability of the oesophageal balloon to reflect intrathoracic pressure changes, it does not ensure that oesophageal pressure will reflect pleural pressure changes in sick premature babies without a pneumothorax. Throughout the study care was taken to position the balloon similarly in each infant. Consequently the measurement at least gave a method of comparison between infants.

Static compliance was measured only in apnoeic ventilated babies and dynamic compliance in spontaneously breathing babies, thus we cannot compare the two measurements. It has been suggested that static compliance may be higher than dynamic compliance measured at the same time.[18] Any effect this might have on our results is reduced by having a similar number of each measurement in the two randomised groups.

Despite possible difficulties with respiratory compliance measurements, our results are comparable with those found by others in premature infants of similar weight.[19] [20] Thus despite relatively high coefficients of variation, this suggests our techniques were as accurate as those used by others. In physiological studies designed to measure respiratory compliance it is possible to control for many of the factors that affect compliance. This is rarely possible in clinical studies. This paper reports comparisons between two randomised groups of ill premature babies who were well matched, apart from surfactant treatment, for the factors that might influence respiratory compliance. As described it was not always possible to measure the respiratory compliance because of equipment failure, neonatal deaths, discharges, or technical difficulties. However, these data losses affected both ALEC treated and control babies to a similar extent. It is therefore valid to compare the overall results from the two groups.

It is possible that saline instilled into the trachea may have altered the respiratory compliance.[21] Any effect of instilling saline would not affect the comparison between the two groups, however, because ALEC was suspended in exactly the same volume of saline as was given to the control babies. Both groups therefore received identical volumes of saline. This volume was used because it was the volume that was considered to be safe for routine endotracheal suction.

This study has shown that artificial surfactant (ALEC) given at birth to babies between 23 and 29 weeks' gestation improves respiratory compliance during the first hours of life so that by 6 hours of age, the ALEC treated babies had a respiratory compliance 69% greater than that of the controls, an effect which persisted at 24 hours. After this the difference in compliance was reduced. This apparent loss of differential effect may be due to three factors. Firstly, more

control babies died during this time (13 controls compared with 10 treated with ALEC) thereby removing more babies with the worst compliance from the control group. Secondly, the compliance in the controls improved slowly during the first few days to reach the level which was achieved in the surfactant treated babies at about six hours. Thirdly, after a few hours the surfactant may have been inhibited by protein exudation on to the alveolar surface[22] or the beneficial effect of ALEC reduced by some other process such as degradation or absorption. If the latter explanation is true, it may be that further doses of surfactant might be beneficial. Interestingly, these changes in compliance are similar to the time course for change in compliance shown in ventilated premature lambs treated with another synthetic surfactant.[23] The effect of ALEC on compliance has a similar time course to the improvements in oxygenation and ventilator pressures which were significantly improved by 12 hours after birth.[4]

Milner *et al* measured compliance at resuscitation in a group of intubated babies after they had received one dose of ALEC, and before and immediately after they were given a second dose, and showed no apparent effect.[24] The results of their measurements are not at variance with this study and again suggest that ALEC takes a few hours to produce its maximum effect after administration at birth.

ALEC had no beneficial effect on the compliance of babies of 30–34 weeks' gestation. The compliance was significantly lower at the one hour measurement in the surfactant treated babies. Many babies in this gestational age group were not very ill. A minority were ventilated and most of those were ventilated for less than one day. Thirty percent did not receive any oxygen, and of those that did receive oxygen 70% had it for less than 72 hours. Exploring the data showed that this effect was present only in babies who were not ventilated. This difference was not seen in the babies less than 30 weeks possibly because most were intubated and ventilated from birth. A possible interpretation of this finding is that surfactant should only be given to those babies who require intubation and ventilation at birth. It is possible that positive pressure ventilation distributes the surfactant to the periphery of the lung whereas in spontaneously breathing babies substantial amounts may remain in the large airways and increase their resistance.

In a non-randomised study Davis *et al* measured respiratory mechanics after administration of calf surfactant extract to premature babies with established respiratory distress syndrome.[1] In 10 ventilated babies, despite improvement in gas exchange, no significant improvement in pulmonary mechanics could be demonstrated. In 25 infants who were only receiving continuous positive airways pressure there was an improvement in compliance.

The artificial surfactant ALEC given at birth to babies under 30 weeks' gestation improves the compliance of the respiratory system by 6 hours of age. This improvement in lung function reflects the lower incidence of respiratory distress syndrome, lower oxygen and ventila-

tory requirements, and reduced mortality seen in babies treated with this artificial surfactant. This simple, protein free surfactant should be a useful addition to the therapeutic weapons of the neonatologist in babies of this age.

1 Davis JM, Veness-Meehan K, Notter RH, Bhutani VK, Kendig JW, Shapiro DL. Changes in pulmonary mechanics after the administration of surfactant to infants with respiratory distress syndrome. *N Engl J Med* 1988; 319:476–9.

2 Morley CJ, Bangham AD, Miller N, Davis JA. Dry artificial surfactant and its effect on very premature babies. *Lancet* 1981;i:64–8.

3 Bangham AD, Morley CJ, Phillips MC. The physical properties of an effective lung surfactant. *Biochim Biophys Acta* 1979;573:552–6.

4 Morley CJ, Gore SM, Greenough A, 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.

5 Morley C, Robertson B, Lachmann B, et al. Artificial surfactant and natural surfactant. Comparative study of the effects on premature rabbits. *Arch Dis Child* 1980;50: 758–65.

6 Morley CJ on behalf of the trial collaborators. Ten centre trial of artificial surfactant (ALEC) in very premature babies. *BMJ* 1987;294:991–6.

7 Thomson A, Elliott J, Silverman M. Pulmonary compliance in sick low birthweight infants. How reliable is oesophageal pressure? *Arch Dis Child* 1983;58:891–6.

8 Pocock SJ. Protocol deviations. *Clinical trials, a practical approach.* Chichester: John Wiley, 1983:176–86.

9 Beardsmore C, Helms P, Stocks J, Hatch DJ, Silverman M. Improved esophageal balloon technique for use in infants. *J Appl Physiol* 1980;49:735–42.

10 Greenough A, Morley CJ. Oesophageal pressure measurements in ventilated preterm babies. *Arch Dis Child* 1982;57: 851–5.

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 a calf lung surfactant extract administered at birth to very premature infants for prevention of respiratory distress syndrome. *Pediatrics* 1985;76:593–9.

13 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.

14 Enhorning G, Shennan A, Possmayer 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.

15 Greenough A, Morley CJ, Davis JA. Interaction of spontaneous respiration with artificial ventilation in preterm babies. *J Pediatr* 1983;103:769–73.

16 Olinsky A, Bryan AC, Bryan MH. A simple method of measuring total respiratory system compliance in newborn infants. *S Afr Med J* 1976;50:128–30.

17 LeSouef PN, Lopes JM, England SJ, Bryan MH, Bryan AC. Influence of chest wall distortion on esophageal pressure. *J Appl Physiol* 1983;55:353–8.

18 Greenough A, Morley CJ, Wood S. Dynamic compliance in ventilated low birthweight babies. *Biol Neonate* 1983;44: 322.

19 LeSouef PN, England SJ, Bryan AC. Total resistance of the respiratory system in preterm infants with and without an endotracheal tube. *J Pediatr* 1984;104:108–11.

20 Simbruner G, Caradello H, Lubec G, Pollak A, Salzer H. Respiratory compliance in newborns after birth and its prognostic value for the course and outcome of respiratory disease. *Respiration* 1982;43:414–23.

21 Lachmann B. Combination of saline instillations with artificial ventilation damages bronchial surfactant. *Lancet* 1987; i:1375.

22 Ikegami M, Jacobs H, Jobe A. Surfactant function in the respiratory distress syndrome. *J Pediatr* 1983;102:443–7.

23 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.

24 Milner AD, Vyas H, Hopkins IE. Effect of exogenous surfactant on total respiratory system compliance. *Arch Dis Child* 1984;59:369–71.

Favouritism and child abuse

Social and cultural differences between nations may make it unsafe to generalise from data derived from one country. Nevertheless a paper from Japan (Tanimura *et al*, *Lancet* 1990; 336:1298–9) provides food for thought about child abuse and there seems to be no a priori reason why the findings shoud not be generally applicable.

One in 10 abused children in a national survey were from multiple births, 15 times the expected rate. In 80% of cases where a twin was abused the other twin was not. The factors leading to abuse for both twins or of only one were different. Abuse of both twins was associated with social, economic, and marital problems and personality disorder in the parents. When one twin was abused that twin was likely to be chronically ill or to have been separated from the parents for a long time, though parental problems were still common. The parents often admitted a strong preference for the other child.

The findings suggest that a potent combination leading to child abuse is parental stress together with some 'unlovable' feature in the child leading to favouritism. Health professionals must be alert to this and the even more important possibility that appropriate intervention might redress the balance and prevent abuse, in singletons as well as in twins.

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