CLINICAL RESEARCH

# Ten centre trial of artificial surfactant (artificial lung expanding compound) in very premature babies

TEN CENTRE STUDY GROUP


## Abstract

**A protein free artificial surfactant (artificial lung expanding compound; ALEC) composed of dipalmitoylphosphatidylcholine and phosphatidylglycerol was assessed for its effect on the main complications of prematurity in a prospective two stage randomised trial of 328 unselected babies delivered at between 25 and 29 weeks of gestation. Babies were randomised to receive approximately 100 mg artificial surfactant suspension or 1 ml saline. This was given at birth into the pharynx with up to three more endotracheal doses if the baby was intubated during the first day. Treatment with artificial surfactant reduced the neonatal mortality from 27% to 14%, the incidence of parenchymal brain haemorrhages from 24% to 16%, and the severity of the respiratory distress syndrome. In the first 10 days babies treated with artificial surfactant who survived averaged 19 hours less in >30% oxygen, 20 hours less ventilation, and 17 hours less supplemental oxygen. Artificial surfactant had no effect on the incidence of pneumothoraces, pulmonary interstitial emphysema, patent ductus arteriosus, or postnatal infections and no serious side effects.**

**Artificial surfactant (ALEC) given to very premature babies at birth significantly reduces their mortality and the respiratory support needed and should prove a valuable addition to treatment.**


TRIAL COLLABORATORS: Dr D Lloyd, Dr P Duffty, Aberdeen Maternity Hospital; Dr G Durbin, Dr I Morgan, Birmingham Maternity Hospital; Dr C Morley, Dr A Greenough, Dr M South, Cambridge Rosie Maternity Hospital; Dr R Hume, Dr T Marshall, Edinburgh Simpson Memorial Maternity Pavilion; Dr T Turner, Dr A Sutton, Glasgow Queen Mother's Hospital; Dr A Greenough, Sister J Poole, Dr H Gamsu, King's College Hospital, London; Dr R Cooke, Dr J Rennie, Liverpool Maternity Hospital; Dr E Hey, Newcastle Princess Mary Maternity Hospital; Dr S Thurlbeck, Dr N McIntosh, St George's Hospital, London; Dr P Dear, Dr D Wheeler, St James's University Hospital, Leeds; Dr S Gore, MRC Biostatistics Unit, Cambridge; Mr N Miller, Dr A Bangham, AFRC Institute of Animal Physiology, Babraham.

Correspondence to: Dr C J Morley, Department of Paediatrics, Addenbrooke's Hospital, Cambridge CB2 2QQ.

## Introduction

Animal or human surfactant extracts placed into the trachea at birth or when respiratory failure is present improve the oxygenation of premature babies and reduce the incidence of severe complications of prematurity.[1-6] "Natural" surfactants, however, may be contaminated with proteins or microbes. A protein free artificial surfactant prepared as a crystalline suspension of phospholipids in cold saline (artificial lung expanding compound; ALEC) has therefore been devised which mimics the monolayer properties of natural surfactant. Details of its formulation and properties and experience of its use have been reported.[7-13]

Two Cambridge based studies have assessed the effect of artificial surfactant given to very premature babies at birth. The first started in September 1979 and used one 25 mg dose of surfactant powder given to intubated babies of under 35 weeks' gestation at birth. At publication in January 1981[10] the mortality was reduced from 24% (8/33 cases) to nil (0/22). The study continued to January 1982, when the overall mortality was reduced from 22% (17/78) to 4% (2/53).[13] The study was criticised, however, for not being randomised.[14] The second study, a randomised controlled trial in Cambridge and Nottingham, ran from January 1982 to May 1985.[13] This used up to 100 mg artificial surfactant suspended in 1 ml cold saline with 1 ml saline as the control substance. Babies were given one dose into the pharynx at birth and up to three further doses if they were intubated during the next 24 hours. That trial was designed to compare respiratory support in the two groups and to randomise 360 babies of less than 35 weeks' gestation. We estimated that the trial would recruit only 90-100 babies of under 30 weeks' gestation and would have only a 50:50 chance of detecting even a halving in their mortality. Babies of 30-34 weeks' gestation already have a low neonatal death rate (about 4%). By May 1984, at interim analysis, data had been collected on 94 babies of 25-29 weeks' gestation; in this group treatment with artificial surfactant had reduced the mortality from 38% (18/47 cases) to 21% (10/47). To

show conclusively whether artificial surfactant was beneficial in this gestational age group a large multicentre trial was carried out. This paper reports the results.

## Subjects and methods

### TRIAL DESIGN

The Cambridge and Nottingham trial was extended to define the effect of artificial surfactant on mortality in babies of 25 to 29 weeks of gestation. This group has a high incidence of the respiratory distress syndrome and a reasonable chance of survival. Secondary targets were the effects on respiratory treatment, severity of the respiratory distress syndrome, and other complications of prematurity.

a new trial had been started some 600 babies would have been required to achieve similar power. A trial including so many babies of between 25 and 29 weeks of gestation would have been very difficult to complete.

Theoretically, extending the trial might have led to results favouring artificial surfactant because the trial was continued in a group of babies in whom artificial surfactant appeared to be effective. Several points, however, should be borne in mind. Firstly, when setting the trial targets most of the collaborators did not know the results of the first stage. Secondly, clinical trials are always based on information which suggests that the trial might be worth while. Thirdly, there are many chance factors which alter the results of a trial; these are minimised when large randomised groups are compared. Lastly, the results of a trial are only estimates of the real effect. Confidence intervals taking into account the possible effect of extending the trial may be calculated theoretically or by simulation. Essentially the procedure slightly reduces the estimated difference in death rates and widens the 95% confidence interval to 2×2·178 standard errors instead of 2×1·96 standard

TABLE I—*Basic data and antenatal factors which might influence outcome*

| | Overall | | 25-26 Weeks | | 27-29 Weeks | |
|---|---|---|---|---|---|---|
| | ALEC | Control | ALEC | Control | ALEC | Control |
| No randomised | 164 | 164 | 46 | 40 | 118 | 124 |
| Ineligible | 5 | 15 | 3 | 8 | 2 | 7 |
| Eligible | 159 | 149 | 43 | 32 | 116 | 117 |
| Non-Cambridge eligible | 89 | 81 | 25 | 17 | 64 | 64 |
| Eligible babies: | | | | | | |
| Mean birth weight in grams (SD) | 1093 (310) | 1070 (251) | 826 (118) | 809 (132) | 1192 (300) | 1141 (228) |
| Mean gestational age in weeks (SD) | 27·6 (1·3) | 27·6 (1·3) | 25·7 (0·4) | 25·5 (0·5) | 28·3 (0·8) | 28·1 (0·8) |
| Boys (%) | 51 | 54 | 72 | 59 | 43 | 52 |
| Membrane rupture >2 days (%) | 23 | 19 | 26 | 25 | 22 | 17 |
| Pre-eclampsia (%) | 17 | 21 | 16 | 13 | 17 | 23 |
| Caesarean section (%) | 58 | 62 | 44 | 38 | 63 | 69 |
| Labour (%) | 67 | 60 | 81 | 81 | 61 | 55 |
| Steroids (%) | 11 | 14 | 12 | 12 | 11 | 14 |
| β Stimulants (%) | 26 | 32 | 35 | 50 | 23 | 27 |
| Multiple birth (%) | 19 | 29 | 21 | 31 | 19 | 28 |
| Intrauterine growth retardation (%) | 15 | 15 | 16 | 3 | 15 | 19 |
| Born infected* (%) | 4 | 6 | 7 | 9 | 3 | 5 |

ALEC=Artificial lung expanding compound (surfactant).
*Baby with bacteria cultured in blood taken at delivery.

TABLE II—*Mortality by gestational age and centre strata. (Denominators for eligible babies only; percentages in parentheses)*

| Gestational age (weeks) | Centre | Neonatal mortality | | Deaths in neonatal unit | |
|---|---|---|---|---|---|
| | | ALEC | Control | ALEC | Control |
| 25-26 | Cambridge | 5/18 (28) | 8/15 (53) | 8/18 (44) | 9/15 (60) |
| | Non-Cambridge* | 8/25 (32) | 7/17 (41) | 11/25 (44) | 7/17 (41) |
| 27-29 | Cambridge | 3/52 (6) | 10/53 (19) | 3/52 (6) | 11/53 (21) |
| | Non-Cambridge* | 7/64 (11) | 15/64 (23) | 8/64 (13) | 17/64 (27) |
| Total | | 23/159 (14) | 40/149 (27) | 30/159 (19) | 44/149 (30) |
| Significance | | $\chi^2$ (accounting for strata)=9·22; p<0·002 | | $\chi^2$ (accounting for strata)=6·95; p<0·01 | |

*Non-Cambridge=All centres other than Cambridge.

At a meeting to plan the trial 12 collaborators were asked their opinions about the possible effect of artificial surfactant on mortality in babies of 25 to 29 weeks of gestation. Without knowing the results of the Cambridge and Nottingham trial they suggested that it might reduce mortality from 36% to 28%. When combined with the opinions of the three Cambridge collaborators who knew the current mortality in the trial the consensus was that a plausible effect of artificial surfactant would be a reduction in mortality from 36% to 27%. A total of 300 eligible babies were required to have a conditional power of 74% for detecting such an effect. This was conditional on including the data in hand from babies of 25 to 29 weeks of gestation in the Cambridge and Nottingham trial. This target would be achieved in one year by collaboration from 10 neonatal units, each randomising about 20 babies, together with the babies of 25 to 29 weeks of gestation from the Cambridge wing of the Cambridge and Nottingham trial. Nottingham did not join this trial.

Extending the Cambridge and Nottingham trial to the multicentre trial was valid because throughout both stages babies were randomised using the same protocol and the Cambridge and Nottingham trial was not large enough to show convincingly clinically significant differences in mortality. If errors (see below). The appendix formalises extending the Cambridge and Nottingham trial to multicentre collaboration and presents the case for debiased confidence intervals, if only extended trials came to publication.

### PROTOCOL

The protocol was identical with that for the Cambridge and Nottingham trial[13] except for the different gestational age criteria and the exclusion of non-resuscitated babies. Babies of 25 to 29 weeks of gestation inclusive were born in hospital, a trial collaborator being present at delivery. Gestation was calculated from the available information. Babies were individually randomised from envelopes immediately before delivery and registered with the biostatistics unit by telephone. Using equipment kept at 4°C, surfactant suspension was prepared just before birth by hand shaking approximately 100 mg with 1 ml saline. Controls received 1 ml saline alone. This volume was chosen because it is the volume that many hospitals use for routine endotracheal lavage. As near to the first breath as possible the baby received

either artificial surfactant or saline into the pharynx so that it might be inhaled. If the baby was intubated for resuscitation a second dose was instilled through the endotracheal tube. If intubated at one and 24 hours third and fourth doses were given. The treatment given was not disclosed to the nurses or doctors caring for the baby. All clinical decisions were taken by the duty paediatric teams. Exclusions were retrospective if the baby was stillborn, resuscitation was not attempted, or the baby had a lethal malformation. The trial was approved by the ethics committee at each hospital. The randomisation ratio was 1:1 by blocks of length 2 or 4 within centre with the two gestational age strata 25 and 26 weeks, and 27, 28, and 29 weeks to prevent imbalance in this influential factor. Twenty randomised babies were later confirmed as ineligible; 15 were controls (three in whom resuscitation was not attempted, four stillborn, eight malformed) and five were in the surfactant treatment group (three stillborn, two malformed).

## ANALYSIS

The trial was designed to assess the effect of artificial surfactant (randomly allocated) on mortality regardless of cause. The Cambridge and non-Cambridge data are separated for comparison because one third of the babies were contributed by Cambridge. For analysis the babies were stratified by gestation and centre: 25-26 weeks Cambridge, 25-26 weeks non-Cambridge; 27-29 weeks Cambridge, 27-29 weeks non-Cambridge. Any difference in the incidence of complications between these strata is reflected in the Mantel-Haenszel analysis,[15] from which the $\chi^2$ values and confidence intervals (1·96×standard error) were derived.[16 17]

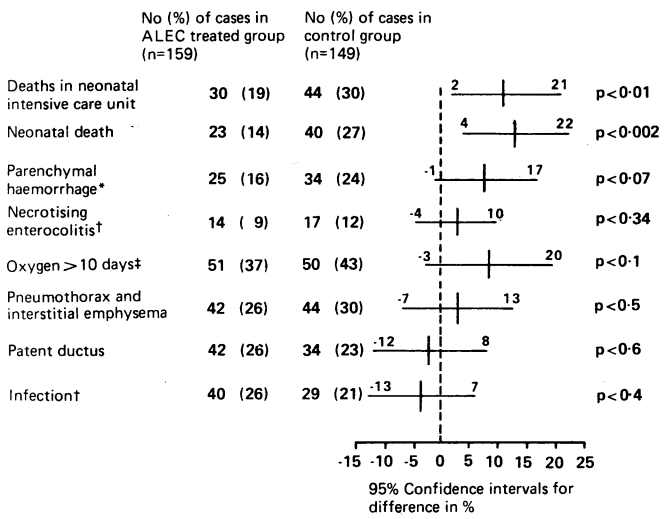


FIG 1—Main complications of prematurity occurring in eligible babies from the two groups and 95% confidence intervals for differences in percentages. p Values for differences take age strata and centres into account.
*Five ALEC treated babies and six controls not scanned.
†As defined, postnatal infection occurred only after first 24 hours; necrotising enterocolitis did not occur in first 24 hours. Denominators were 152 ALEC treated babies and 139 controls.
‡A total of 138 ALEC treated babies and 117 controls survived 10 days.

Before the trial data from previous studies were used to grade the respiratory distress syndrome by the number of hours each baby received >30% oxygen in the first 10 days: <24 hours, none; 24-47 hours, mild; 48-120 hours, moderate; >120 hours, severe. Deaths in the first five days were graded as severe respiratory distress syndrome if a baby died receiving >30% oxygen. If a baby died after five days the grading was as above. Ventilation was not used in the grading because 80% of very premature babies are ventilated from birth even though some do not have the respiratory distress syndrome. An oxygen concentration of 30% was chosen as cut off because many premature babies require low concentrations of oxygen for long periods to treat problems unrelated to the respiratory distress syndrome.

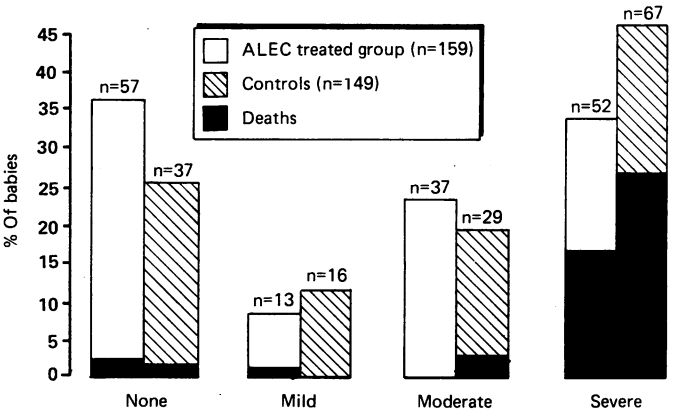


FIG 2—Grades of respiratory distress syndrome and proportions of deaths in ALEC treated and control groups.
$\chi^2$ For trend (severity ordered as 0, 1, 2, 3)=4·84; p<0·03.

The analysis compared babies in the groups to which they were randomised. Four babies were not treated as randomised; a pair of twins was muddled, one baby was given saline instead of artificial surfactant, and one envelope was wrongly coded.

## Results

Three hundred and twenty eight babies were randomised to receive saline alone or the artificial surfactant (ALEC), of whom 20 were ineligible for further analysis. Table I shows the groups by gestational age and the distribution of antenatal factors which could influence the incidence of complications. There was a reasonable balance between groups, except for an excess of multiple births among the controls. This was allowed for in the regression analyses. The number of babies randomised in the 10 centres were: Aberdeen 27; Birmingham 17; Edinburgh 12; Glasgow 21; King's, London, 24; Leeds 27; Liverpool 22; Newcastle 19; St George's, London, 12; Cambridge 147 (of these, 124 were randomised in the Cambridge and Nottingham trial, 77 before the decision to extend).

Figure 1 shows the main complications of prematurity with 95% confidence intervals and p values from the Mantel-Haenszel analysis. The results between the strata were not significantly different for any complication, though given the numbers studied the $\chi^2_{(3)}$ test for heterogeneity had low power.[17]

## MORTALITY

Treatment with artificial surfactant reduced neonatal mortality (first 28 days) from 27% (40/149 cases) to 14% (23/159) (p<0·002), the 95% confidence interval being four to 22 additional neonatal survivors per 100 surfactant treated infants. There were no significant differences with treatment between Cambridge (controls 26% (18/68), surfactant group 11% (8/70)) and non-Cambridge centres (controls 27% (22/81), surfactant group 17% (15/89)) and by gestation (25-26 weeks: controls 47% (15/32), surfactant group 30% (13/43); 27-29 weeks: controls 21% (25/117), surfactant group 9% (10/116)) (table II). The overall effect of artificial surfactant on mortality was equivalent to the babies being older by over one week of gestation and better than being female (table III).

Mortality while in the neonatal unit was reduced from 30% (44/149 cases) to 19% (30/159) (p<0·01), the 95% confidence interval being two to 21 extra survivors per 100 treated babies. There were no significant differences with treatment between Cambridge (controls 29% (20/68), surfactant group 16% (11/70)) and non-Cambridge centres (controls 30% (24/81), surfactant group 21% (18/89)) and by gestation (25-26 weeks: controls 50% (16/32), surfactant group 44% (19/43); 27-29 weeks: controls 24% (28/117), surfactant group 9% (11/118)) (table II).

If allowance is made for a possible influence from the two stage trial design a more conservative analysis using simulation adjusted 95% confidence intervals for mortality would be: neonatal mortality, one to 21 additional neonatal survivors per 100 surfactant treated infants; mortality while in the neonatal unit, one less to 19 extra survivors per 100 surfactant treated babies.

No statistical adjustment was made for the two stage trial design except for mortality, for which both adjusted and unadjusted confidence intervals are cited. Throughout p values are not adjusted.

Regression analysis for neonatal mortality, hours of ventilation, hours receiving oxygen, and hours receiving >30% oxygen during the first 240 hours for survivors at 10 days compared the effect of artificial surfactant with the effect of being female or having one extra week of gestation. Adjustment was also made for centre and multiple birth because of imbalance in this factor. Ten days was chosen because effects of surfactant should be apparent during this time and it reduced the data collected.

As more surfactant treated than control babies survive more may have complications, which may bias the analysis of these complications against artificial surfactant.

TABLE III—*Effect of prognostic factors on neonatal mortality*

| Prognostic factor | Coefficient | SE | p Value |
|---|---|---|---|
| ALEC | −0·71 | 0·26 | <0·005 |
| Female | −0·31 | 0·27 | <0·25 |
| Each additional week of gestational age | −0·50 | 0·10 | <0·0001 |
| 1st Multiple | −0·03 | 0·44 | NS |
| 2nd Or more multiple | −0·17 | 0·39 | NS |
| Non-Cambridge | 0·07 | 0·26 | NS |

Coefficients (natural logarithm of relative risk of neonatal death) give comparative effect of each prognostic factor on chance of neonatal death. Baseline for analysis with each factor having coefficient of 0 is: control, male, gestation 27·6 weeks (average of trial), singleton, born in Cambridge. To give risk score for any baby coefficients may be added—for example, compared with baseline control baby with score of zero a surfactant treated (−0·71) female (−0·31) singleton (0) born one week older (−0·50) in non-Cambridge centre (0·07) would have reduced risk of neonatal death—that is, composite score −1·45 (one quarter of relative risk; exponential −1·45=0·23).

(p<0·14) than the controls. These effects were similar to the reduction produced by one extra week of gestational age (table IV).

Four (3%) babies in each group required no additional oxygen; 20 (13%) surfactant treated babies and 14 (9%) controls needed no ventilation, and 11 (7%) surfactant treated babies and 13 (9%) controls required less than 30% oxygen.

### PNEUMOTHORAX OR GROSS PULMONARY INTERSTITIAL EMPHYSEMA

Pneumothorax and gross interstitial emphysema occurred in 26% (42/159) of surfactant treated babies and 30% (44/149) of the controls ($\chi^2$=0·45; NS) (fig 1).

### PATENT DUCTUS ARTERIOSUS

Patent ductus arteriosus was diagnosed from a classical murmur, bounding pulses, plethoric lung fields, and the need for treatment. A patent ductus was found in 26% (42/159) of the surfactant treated group and 23% (34/149) of the controls ($\chi^2$=0·30; NS) (fig 1).

TABLE IV—*Effect of prognostic factors on respiratory support in first 10 days. Survivors only*

| | Hours of oxygen | | | Hours of >30% oxygen | | | Hours of intermittent positive pressure ventilation | | |
|---|---|---|---|---|---|---|---|---|---|
| Prognostic factor | Coefficient | SE | p Value | Coefficient | SE | p Value | Coefficient | SE | p Value |
| ALEC | −16·6 | 11·1 | <0·14 | −18·7 | 9·5 | <0·05 | −20·2 | 10·1 | <0·05 |
| Female | −5·1 | 11·3 | NS | −4·7 | 9·6 | NS | −2·1 | 10·3 | NS |
| Each additional week of gestational age | −20·9 | 4·4 | <0·0001 | −16·8 | 3·7 | <0·0001 | −31·4 | 4·0 | <0·0001 |
| 1st Multiple | −9·9 | 17·6 | NS | −8·5 | 15·0 | NS | −14·0 | 16·0 | NS |
| 2nd Or more multiple | 42·7 | 16·4 | <0·01 | 20·2 | 14·0 | <0·15 | 56·6 | 15·0 | <0·0002 |
| Non-Cambridge | −1·5 | 11·3 | NS | 9·9 | 9·7 | NS | 30·5 | 10·3 | <0·003 |
| Baseline (hours)* | | 197·1 | | | 128·8 | | | 183·4 | |

*Baseline is respiratory support required by male singleton control at 25 weeks' gestation in Cambridge.
For explanation of multiple regression analysis see table III. Coefficients may be considered as change in hours of support attributable to each prognostic factor in first 10 days compared with baseline.

### PERIVENTRICULAR HAEMORRHAGE

Parenchymal brain haemorrhages were detected by ultrasonography or at necropsy. Ultrasound grading was not standardised among centres, so haemorrhages were recorded as no bleeding, bleeding but not parenchymal, and parenchymal brain haemorrhage. Five surfactant treated and six control babies were not scanned. The analysis concentrates on parenchymal haemorrhages because these are associated with developmental problems.[18]

The incidence of parenchymal haemorrhages (fig 1) was reduced by surfactant from 24% (34/143 cases) to 16% (25/154) ($\chi^2$=3·43; p=0·06) with a 95% confidence interval of one extra to 17 fewer parenchymal haemorrhages per 100 surfactant treated babies. There was no significant heterogeneity among strata ($\chi^2_{(3)}$=4·38) in Cambridge (controls 30% (20/67), surfactant group 14% (10/70)) and non-Cambridge centres (controls 18% (14/76), surfactant group 18% (15/84)) and by gestation of 25-26 weeks: controls 32% (10/31), surfactant group 33% (14/42); 27-29 weeks: controls 21% (24/112), surfactant group 10% (11/112)). The incidence of non-parenchymal haemorrhage was 19% in the two groups.

### RESPIRATORY DISTRESS SYNDROME

Figure 2 shows the grades of respiratory distress syndrome; 36% (57/159) of surfactant treated babies had no respiratory distress compared with 25% (37/149) of the controls, and 45% (67/149) of the controls had severe respiratory distress compared with 33% (52/159) of the surfactant treated babies. Trend analysis regressing the surfactant treated proportions in each grade on ordered severity was consistent with more surfactant treated babies in the less severe grades ($\chi^2$ for trend=4·84; p<0·03).

### RESPIRATORY SUPPORT IN FIRST 10 DAYS (SURVIVORS ONLY)

Surfactant treated babies had on average 19 hours less in >30% oxygen (p<0·05), 20 hours less ventilation (p<0·05), and 17 hours less oxygen

### PROLONGED OXYGEN TREATMENT

Oxygen treatment beyond 10 days (that is, on the 11th day) was required by 43% (50/117) of the controls and 37% (51/138) of the surfactant treated babies ($\chi^2$=2·58; NS); 95% confidence interval was three extra to 20 fewer cases per 100 treated babies (fig 1).

### NECROTISING ENTEROCOLITIS

Necrotising enterocolitis was diagnosed when babies had distension and bloody stools of no other obvious cause. The incidence in the two groups was similar: controls 12% (17/139), surfactant treated babies 9% (14/152) ($\chi^2$=0·90; NS) (fig 1).

### SERIOUS INFECTIONS NOT PRESENT AT BIRTH

Serious infections that occurred more than 24 hours after delivery included bacteriologically proved meningitis, pneumonia, and septicaemia. Analysis was therefore restricted to babies who survived at least 24 hours. The incidence in surfactant treated babies was similar to that in the controls (26% (40/152) *v* 21% (29/139); $\chi^2$=0·58, NS). Five babies in each group had pneumonia in the first week. Other infections were due to various different organisms and occurred over many weeks (fig 1).

## Discussion

In the Cambridge and Nottingham trial artificial surfactant (artificial lung expanding compound; ALEC) given to babies of under 30 weeks' gestation significantly reduced the oxygen requirements and ventilatory pressures needed during the first few days[13] and significantly improved compliance of the respiratory

system at six hours (data to be published). This trial shows that artificial surfactant reduces the mortality by a third. The trials were designed to assess the effect of artificial surfactant as used in routine clinical practice. Babies entered the trial purely on the basis of gestational age with all the complicating factors of prematurity—asphyxia, infection, hydrops fetalis, antepartum haemorrhage, prolonged rupture of the membranes, severe toxaemia, or even with mature lungs. Compared with trials in which babies were selected[3-6] any effect of artificial surfactant in this trial could be masked by the deleterious effect of the perinatal complications. It therefore gives a more realistic estimate of the clinical benefits of surfactant.

Mortality was chosen as the primary outcome for the trial because it is unambiguous and high enough in very premature babies (36%) to allow a reduction to be detected, given reasonable numbers. The trial showed an effect on mortality consistent with that found in other studies of the artificial surfactant (ALEC).[10 13 19] It has been suggested that this artificial surfactant is not so effective as natural surfactant preparations.[19-21] Analysis of the comparative effect on mortality of different surfactants in different clinical trials (table V), however, showed that when the 95% confidence intervals for the effect on mortality were compared the protein free artificial surfactant was at least as efficacious in terms of mortality as the more complicated natural surfactant preparations, particularly when gestational age, perinatal complications, and different trial exclusion criteria were taken into account. From a trial of this size we cannot comment confidently on the effect of the artificial surfactant in babies of different gestational ages, though our impression is that it is more effective in babies of 27 to 29 weeks of gestation.

Several studies have shown that exogenous surfactants given either at birth[5 10 13] or to babies after the onset of respiratory difficulties[1 3 4 6] reduce the need for high inspired oxygen concentrations and the incidence of serious complications. The different surfactant preparations used in comparatively small, often preselected groups of babies and the varied timing and doses of surfactant given make it difficult to compare the trials. The effect of artificial surfactant on oxygenation, however, has already been shown,[13] and in this trial artificial surfactant significantly reduced the severity of the respiratory distress syndrome.

The premature baby's lung is immature in most aspects of its structure and function, with small numbers of poorly vascularised air sacs, difficulty clearing fluid after birth, and an epithelium which is easily damaged, causing protein exudation on to the lung surface, which interferes with gas transfer and inhibits the function of surfactant. Not surprisingly, therefore, trials of exogenous surfactant have invariably been only partially effective in ameliorating neonatal respiratory problems.

Giving surfactant to babies at birth means that they are treated before the possible onset of the respiratory distress syndrome. It is important that it should do no harm. Artificial surfactant (ALEC) is unlikely to be harmful because (*a*) the two components are similar to the phospholipids which are deficient in the premature lung, (*b*) saturated phospholipids are bacteriostatic, (*c*) the process by which it is formulated ensures sterility, and (*d*) there is no protein component which might sensitise the baby. In the trials to date this artificial surfactant appears to be without harmful effects, though larger numbers will be needed for complete assurance. Given the numbers of babies treated rare side effects would not be detected. One baby was reported to have a temporarily blocked endotracheal tube after the instillation of surfactant; though an isolated incident, this might be avoided by delivering the dose in small aliquots.

Combining all the randomised and non-randomised trials of artificial surfactant (ALEC) gives a total of 323 babies who have been treated and 334 controls and shows an overall reduction in mortality of 42%—that is, from 19% (62/334) to 11% (36/323).

TABLE V—*Comparative effect of different surfactant preparations on mortality in prophylactic clinical trials documenting deaths*

| Reference | Surfactant | Gestational age (weeks) | Controls | | Surfactant | | Reduction in deaths/100 treated babies | |
|---|---|---|---|---|---|---|---|---|
| | | | No | % Dead | No | % Dead | Reduction | 95% Confidence interval |
| Merritt *et al*[6]* | Human | 24-29 | 29 | 52 | 31 | 16 | 36 | 14 to 58 |
| Enhorning *et al*[3]* | Calf | <30 | 33 | 21 | 39 | 3 | 18 | 3 to 33 |
| Halliday *et al*[22]† | DPPC+HDL | 27-29 | 14 | 43 | 16 | 25 | 18 | −15 to 51 |
| Halliday *et al*[22]† | DPPC+HDL | 25, 26, 30-33 | 37 | 0 | 33 | 6 | −6 | −14 to 2 |
| Kwong *et al*[4]† | Calf | 24-28 | 13 | 15 | 14 | 7 | 8 | −16 to 32 |
| Shapiro *et al*[5]† | Calf | 25-29 | 16 | | 16 | | Reported as no difference | |
| Morley[13]† | ALEC dry | <30 | 35 | 44 | 28 | 7 | 37 | 18 to 56 |
| Morley[13]† | ALEC dry | 31-34 | 43 | 5 | 25 | 0 | 5 | −2 to 12 |
| Wilkinson *et al*[19]* | ALEC dry | <31 | 12 | 17 | 12 | 0 | 17 | −5 to 39 |
| Cambridge and Nottingham trial[13]† | ALEC | <25, >29 | 98 | 1 | 98 | 4 | −3 | −7 to 1 |
| Cambridge and Nottingham trial[13]† | ALEC | 25-29 | 67 | 34 | 69 | 19 | 15 | 1 to 31 |
| Present trial* | ALEC | 25-29 | 149 | 27 | 159 | 14 | 13 | 4 to 22 |

True effect of each surfactant lies between 95% confidence intervals. Control mortality varied greatly among trials owing to different gestational ages and exclusion criteria. Trials by Halliday *et al*[22] and Morley[13] and Cambridge and Nottingham trial[13] are divided into two subsets of babies of early and late gestation for comparison with trials studying babies in early gestational age range only. Present trial included babies from Cambridge and Nottingham trial.
DPPC+HDL=Dipalmitoylphosphatidylcholine+high density lipoprotein.
*Neonatal mortality.
†Overall mortality.

The multicentre design of this trial adds robustness to the results, which show that treatment at birth with this protein free artificial surfactant significantly reduces the mortality and respiratory support needed in very premature babies and has no serious side effects. It should therefore be a useful addition to the treatment of premature babies.

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## Appendix

SEQUENTIAL TRIAL EXTENSION AND CASE FOR DEBIASED CONFIDENCE INTERVALS

Extending the Cambridge and Nottingham trial to multicentre collaboration to compare mortality between surfactant (ALEC) treated and control infants of 25-29 weeks' gestation may be formalised as follows.

*Stage 1*—Randomised 80 babies.

*Continuation criterion*—For continuation of trial mortality differential must be at least 1 SE in favour of surfactant. (If surfactant does not reduce mortality there is 16% risk of continuation; if surfactant reduces mortality by one third the chance of continuation is at least 50%.)

*Stage 2*—If continuation criterion is met randomise a further 240 babies; otherwise terminate recruitment.

The continuation criterion was not preset for extending to stage 2, and so the above design has been simulated also with less liberal continuation criteria: 1·28 SE and 1·64 SE to ascertain by how much, on average, the observed reduction in death rates reported in extended trials—that is, those which randomised 80+240 infants—overestimates the actual difference in death rates. Intuitively the bias will be small when the experimental treatment is effective because it will not be exceptional for the continuation criterion to be met, whereas if a new treatment was not an improvement over the control then we are relying on stage 2 recruitment of a further 240 infants to redress the fortuitous stage 1 differential. Had the stage 2 recruitment been greater then biases would be correspondingly smaller. Thus an appropriate debiasing procedure in sequential trials depends on design and whether all trials or only extended trials come to publication. Debiased confidence intervals, appropriate if only stage 2 trials were published, have been derived by simulation of the above design formulation, in which control mortality was specified as 36%, 30%, or 27% and mortality after surfactant given by nil, a quarter, or one third reduction on the control death rate. Debiased 95% confidence intervals for the difference in death rates (control-surfactant), besides being shifted towards zero (by roughly two deaths per 100 surfactant treated babies when surfactant induces a one third reduction in mortality), have a width 2×2·178 SE instead of 2×1·97 SE (table VI).

TABLE VI—*Confidence intervals appropriate if only trials extended to stage 2 were published*

| | | | 95% Confidence interval reduction in deaths/100 babies | | | |
|---|---|---|---|---|---|---|
| | Death rates (%) | | Biased | | Unbiased | |
| Outcome | Control | ALEC | Reduction | Confidence interval | Reduction | Confidence interval |
| As randomised, no exclusions | 36 | 21 | 15·0 | 6 to 24 | 13·5 | 3 to 24 |
| As randomised, eligible babies | 30 | 29 | 11·0 | 2 to 21 | 9·0 | −1 to 19 |
| As randomised, eligible babies, neonatal deaths | 27 | 14 | 13·0 | 4 to 22 | 11·5 | 1 to 21 |

## 100 YEARS AGO

MR. JUSTICE KAY, in announcing judgment in a case brought by a seller of quack medicines against one of the same fraternity for the infringement of trade mark, said lest either party should be tempted to make the judgment a useful medium for advertising his article, he hoped he would add to the advertisement the following intimation, "No one should use this preparation except under medical advice." (*British Medical Journal* 1887;ii:1121.)

As the science of medicine becomes more differentiated, new terms come into use, and there is a tendency to restrict more and more the use of the older ones. This, although a great saving of trouble to the expert, occasionally causes some confusion to the novice, or to those who have allowed their knowledge to fall behind the time. Some years ago the terms amaurosis and glaucoma were frequently applied to conditions to which no one now would attach them. There is now a tendency to restrict further the application of the term hemiopia, and to employ it only for cases in which the lesion is obviously not intra-ocular. The loss of one half of the visual field may of course occur from an intra-ocular lesion, such as a haemorrhage, or detachment of the retina, but in such cases the boundary line between the blind and the seeing portions of the field hardly ever coincides with the middle of the field, and is generally irregular, while the condition is usually uni-ocular. Although such a condition might be called hemiopia of one eye, and was formerly frequently so designated, it is now more usual to speak in such a case of a loss of the upper or lower portion of the visual field, etc., and to restrict the term hemiopia to cases in which the line of separation is vertical or nearly so, and nearly bisects the field. The terms hemianopia, hemianopsia, hemiopia, are used indifferently to express the same condition, and with English writers hemiopia is the favourite. Since hemianopia or hemianopsia means that one half of each visual field is blind, the terms left, right, temporal, and nasal hemianopia would respectively indicate that there was loss of function over the portions of the field named. The term hemiopia, or half sight, is, it must be remembered, used in exactly the same way, and although the word itself does not, as in the previous instance, indicate it, "left hemiopia," etc., also means a loss of the half of the field named. The term "homonymous hemianopsia," is sometimes used to express the fact that in both the fields the defect is to the same side of the middle line, and "crossed hemianopsia" to indicate a bilateral, temporal, or nasal, defect. "Complete hemianopsia" means that the entire half of the field is affected; the term "absolute," that the blindness over the affected area is total. Another term, which is of comparatively recent origin, is "word-blindness" (alexia, or dyslexia) a condition in which with perfect vision there is an inability to comprehend the meaning of word-symbols; obviously this is closely allied to aphasia, but not neccessarily associated with it. (*British Medical Journal* 1887;ii:81.)