Follow up of premature babies treated with artificial surfactant (ALEC)

C J Morley, R Morley

Abstract
Of 235 survivors who had taken part in a randomised trial of artificial surfactant and who were born in Cambridge, follow up information was available for 231 (98%) infants. In 12 cases information came from local doctors; all others were assessed at 9 and 18 months (n=212) or 9 months only (n=7). There was no difference between those who had been treated with surfactant and control babies in the incidence of neurologic impairment, mental impairment, respiratory infections, allergies, or hospital admissions up to 18 months after full term. In those born before 30 weeks’ gestation (where surfactant most improves survival) the number of surviving randomised children who were normal was 35 of 61 in the treated group (57%) compared with 25 of 61 in the control group (41%). Improved neonatal survival after prophylactic surfactant treatment is not associated with an increased incidence of neurodevelopmental impairment.

Artificial surfactant (artificial lung expanding compound, Pumactant, Britannia Pharmaceuticals) composed of dipalmitoylphosphatidylcholine and unsaturated phosphatidylglycerol in a ratio of 7:3 has been used successfully in one case controlled study1 2 and two randomised control trials.3 4 In the last of these, a multicentre trial, a reduction in neonatal mortality for babies between 25 and 29 weeks’ gestation, from 27% to 14% was shown. There was also a reduction of one third in the incidence of parenchymal brain haemorrhages from 24% to 16%, and a significant reduction in the need for more than 30% oxygen and the amount of artificial ventilation required. There has been concern that improved survival of these very premature babies may result in an increased number of impaired children. This trial presents the follow up of the survivors treated in Cambridge from the first randomised trial.3

Patients and methods
All surviving children from the trial were invited for follow up examinations by RM 9 and 18 months after their expected date of delivery. The examiner did not know any details about the infants’ neonatal progress, nor whether they had been randomised to receive treatment with surfactant or to be controls. At 9 months a medical history and full physical examination were undertaken, including the neurological examination described by Amiel-Tison and Grenier.5 The developmental screening inventory described by Knobloch et al was also used.6 The score for each area of development was derived from the child’s age corrected for prematurity (that is, chronologcal age minus the time from delivery to expected date of delivery). An overall development quotient was calculated as the mean of the quotients for the individual areas (adaptive, motor, fine motor, language, and personal/social).

At 18 months a history was taken and the child had another physical examination. The Bayley mental and motor scales were administered and the mental and motor development index and psychomotor development index calculated.7 The mental scale, like most tests of intellectual development in small children, relies heavily on fine motor skills appropriate for age. In children with cerebral palsy, therefore, the results often bear little relation to intellectual prowess. The academic scale of Developmental Profile II8 for which an intelligence quotient (IQ) equivalent can be calculated relies little on fine motor skills at this age, so it was used for all infants in addition to the Bayley mental scale. Scores for all these tests were also calculated for the age corrected for prematurity. Mental impairment was diagnosed when the child’s score was more than two standard deviations below the population mean. Social class of the family was coded using the Registrar General’s classification, social class III being subdivided into non-manual and manual.9 The child’s rank was recorded as his birth order in the living children in the family, with twins assigned equal rank. Student’s t test, the χ² test, and linear regression were used for statistical analysis of the results.

Results
Of 276 eligible infants included in the surfactant trial, 244 (119 controls and 125 treated with surfactant) survived to leave the neonatal unit. Nine of these infants died later, five controls (two of chronic lung disease, one of sudden infant death syndrome (SIDS), one of Wilms’ tumour, and one of toxic shock syndrome), and four treated with surfactant (three of chronic lung disease, and one of SIDS). There were 235 babies eligible for follow up. Four were lost to follow up: all were children whose parents had been posted overseas. They were all girls and included one control and three who had been treated with surfactant; none were born at less than 30 weeks’ gestation. It was not known whether they survived. In total, 231 infants were known to survive to 18 months after full

Department of Paediatrics, Level 8, Addenbrooke’s Hospital, Hills Road, Cambridge CB2 2QQ C J Morley Medical Research Council Dunn Nutrition Unit, Cambridge R Morley Correspondence to: Dr C J Morley. Accepted 26 March 1990

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CHILDREN BORN AT LESS THAN 30 WEEKS' GESTATION

Of the 122 infants born at less than 30 weeks' gestation who entered the trial (61 in each group) there were 85 survivors who were all seen or reported on at 18 months (47 treated and 38 controls).

OUTCOME OF CHILDREN NOT SEEN AT FOLLOW UP

Ten of the 12 children who were not seen by RM were reported to be developmentally normal (five in each group): of the other two, one (a control) was reported to have mild spastic diplegia but not mental impairment and the other (a treated baby) was microcephalic and mentally impaired.

OUTCOME OF CHILDREN SEEN ONLY AT 9 MONTHS

Of the seven infants seen only at 9 months, six had developmental quotients well within the normal range; they were reported as developmentally normal at 18 months. One, a control infant, had Prader-Willi syndrome and was mentally impaired; he was excluded from analysis of mental impairment as his impairment was the result of a recognised congenital abnormality.

NEUROLOGICAL OUTCOME

Twenty-three children were diagnosed as having neurological impairment: nine of 114 were controls (8%) and 14 of 117 had been treated with surfactant (12%).

Among the infants of less than 30 weeks' gestation, neurological impairment was diagnosed in six of 38 controls (16%) and nine of 47 treated infants (19%), and in those of 30 weeks' gestation or more the incidence was three of 76 among the controls (4%) and five of 70 in the treated infants (7%). There was no significant difference between treated and control children.

Severity of impairment was assessed functionally. Thus children not able to sit unsupported at 18 months were classified as 'severely impaired', those not able to pull up to standing or walk with hands held as 'moderately impaired', and those able to do all these things but having abnormal neurological signs as 'mildly impaired'. In the control group impairments were: severe (n=4), moderate (n=1), mild (n=4), compared with severe (n=7), moderate (n=2), and mild (n=5) in the treated group. In the babies born before 30 weeks' gestation the impairments were: severe (n=3), moderate (n=1), mild (n=2) among the controls, and severe (n=5), moderate (n=1), mild (n=3) in those who were treated.

DEVELOPMENTAL OUTCOME

Mean scores for the Bayley mental scale, Bayley motor scale and academic scale of Developmental Profile II (IQ equivalent) are shown in table 1. These results are for the 212 infants seen by RM at 18 months after full term. There are no significant differences between the mean scores of children from control and treated groups for the whole cohort or for the babies of less than 30 weeks' gestation.

Developmental outcome is considerably influenced by social and demographic factors. To be certain that any minor imbalances were not biasing the results, the scores for all infants were entered into multiple regression analysis as dependent variables. Independent factors included in the models were treatment with surfactant and pre-existing factors at randomisation: sex, gestation, social class, and birth rank. The results confirmed that surfactant treatment was not significantly related to the Bayley mental scale, IQ equivalent, or Bayley motor scale in the whole group or in those above and below 30 weeks' gestation, whether or not children with neurological impairment were included.

In neurologically normal infants, five of 105 controls (5%) controls were diagnosed as mentally impaired (Bayley mental development index >70 in those tested by RM) compared with nine of 103 treated infants (4%). The incidence in babies of less than 30 weeks' gestation was three of 38 controls (8%) and two of 47 treated babies (4%).

NORMAL SURVIVAL IN BABIES BORN AT LESS THAN 30 WEEKS' GESTATION

In the surviving children born before 30 weeks' gestation, in whom mortality was significantly reduced by prophylactic treatment with artificial surfactant (ALEC), treated children had no

<table>
<thead>
<tr>
<th>All infants</th>
<th>Infants of &lt;30 weeks' gestation</th>
<th>Infants of ≥30 weeks' gestation</th>
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<tbody>
<tr>
<td>All infants</td>
<td>Controls (n=107)</td>
<td>Surfactant (n=105)</td>
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<tr>
<td>Bayley mental development index*</td>
<td>104 (21)</td>
<td>101 (18)</td>
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<tr>
<td>Bayley motor development index*</td>
<td>107 (18)</td>
<td>105 (19)</td>
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<tr>
<td>IQ equivalent</td>
<td>93 (16)</td>
<td>93 (15)</td>
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*Scores for children with neurological impairment are excluded.
The number of children had more than one hearing loss or otitis media. Some children had more than one respiratory infection. The number of normal survivors was 57% in the control group and 66% in the group treated with surfactant. The difference was significant (p=0.07). Children in the treated group did not differ from controls in their later requirements for admission to hospital or treatment of respiratory or middle ear infections, nor in their incidence of allergic reactions.

Trends of very premature infants with prophylactic artificial surfactant (ALEC), significantly improved neonatal mortality, with no increase in the rate of neurodevelopmental impairment, respiratory illness, or allergies.

Discussion

Three trials of this surfactant have shown reductions in neonatal mortality and the incidence of brain haemorrhages. As such premature babies are at high risk of neurological or mental impairment, we were concerned that the increased survival of those very premature babies who were treated could lead to an increase in the number of impaired survivors.

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