Retinopathy of prematurity in a controlled trial of prophylactic surfactant treatment

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Abstract

Aims—To investigate the incidence of acute and cicatricial retinopathy of prematurity (ROP) in a cohort of premature neonates entered into a randomised, multicentre trial of prophylactic exogenous surfactant for respiratory distress syndrome (RDS) compared with controls receiving surfactant only if severe RDS developed.

Methods—The incidence of acute and cicatricial ROP was assessed in 304 neonates born at less than 30 weeks' gestation in a geographically defined population of approximately three million.

Results—There was a trend towards improved survival in the group receiving prophylactic surfactant with 102/151 (67.5%) surviving compared with 82/141 controls (58.2%, $p=0.12$). The prophylactic surfactant group would be expected to have an increased risk of ROP due to improved survival, particularly of the most premature infants. However, there was no statistically significant difference in the incidence of acute ROP between the two groups and the incidence of cicatricial ROP was lower in the group receiving prophylactic surfactant (4/100 survivors, 4.0%) compared with neonates receiving rescue surfactant as required (6/81, 7.4%). This difference did not reach statistical significance ($p=0.35$).

Conclusion—The trend for a lower incidence of cicatricial ROP in those neonates treated with prophylactic surfactant compared with the rescue surfactant group, despite improved survival, suggests that the use of prophylactic surfactant also had a beneficial effect on the development of cicatricial ROP.

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The present epidemic of retinopathy of prematurity (ROP) is attributed to the increased survival of very premature infants.¹ The survival of very premature neonates has been significantly improved by the use of exogenous surfactant to treat respiratory distress syndrome (RDS).² RDS is due to deficiency of surfactant which is a complex mixture of phospholipids and proteins, produced in the lungs, which reduces the surface tension and so prevents alveolar collapse. Very premature babies treated with surfactant for RDS have a marked improvement in morbidity as well as mortality.³

The aetiology of ROP is uncertain. One important factor is gestational age which is inversely related to the incidence of ROP.⁴⁻⁷ If

gestational age were the sole factor influencing the incidence of ROP then one would expect that the increased survival due to surfactant use would result in an increased incidence of ROP. On the other hand, if respiratory health and homeostasis are also significant determinants of ROP development, then the use of surfactant would be expected to reduce the gestational age-adjusted incidence of ROP. The effect of surfactant upon the overall incidence of ROP would then be determined by the balance of these two opposing effects.

More recently, exogenous surfactant has been used prophylactically in those neonates most at risk of developing RDS. During 1990 and 1991 a multicentre, randomised controlled trial (OSIRIS) compared neonates who received prophylactic surfactant within 2 hours of birth with a control group of neonates who received surfactant treatment only if they developed severe RDS ('rescue' treatment).⁸ This trial studied 2690 neonates and demonstrated that prophylactic surfactant markedly improved morbidity and mortality with a 16% decrease in death or chronic oxygen dependence at term. The markedly improved survival of premature neonates treated prophylactically with surfactant means that it would now be unethical to perform a prospective randomised trial of prophylactic surfactant. However, the neonates in the OSIRIS trial comprise a suitably randomised cohort, the survivors of which are available for examination.

This paper presents the results of examination of a regionally defined subset of the neonates in the OSIRIS trial, undertaken to determine the effect of prophylactic surfactant administration upon the incidence of ROP in very premature neonates.

Methods

The details of the controlled trial of prophylactic surfactant are published.⁸ In summary, all neonates born at less than 30 weeks' gestation were eligible for inclusion in the OSIRIS trial if the following criteria were met: (1) already intubated to receive respiratory support; (2) no congenital abnormality; (3) parental consent had been given; and (4) randomised before 2 hours old.

Patients were randomised by the Oxford clinical trials service into prophylactic and rescue surfactant groups, with optimum matching for: (1) gestational age, (2) sex, (3) hospital delivered, (4) single/multiple pregnancy, (5) prenatal dexamethasone.

For ethical reasons it was not possible to design a trial in which one group of neonates

was denied surfactant therapy. Instead the neonates were allocated randomly to either prophylactic or rescue surfactant groups.

PROPHYLACTIC SURFACTANT GROUP

Patients randomised to this group received prophylactic synthetic surfactant (Exosurf) 5 ml/kg as a bolus within 2 hours of birth with a further dose 12 hours later.

RESCUE SURFACTANT GROUP

These neonates received the same surfactant treatment only if clinical RDS developed with an arterial/alveolar oxygen partial pressure (a/A) ratio of <0.22 .

Within both prophylactic and rescue groups there was further randomisation of neonates to receive only two doses of surfactant (as described above) or to receive a further two doses if RDS failed to resolve after the first two doses. The multicentre trial⁷ showed no difference in outcome for the two and four bolus subgroups in either the prophylactic or rescue surfactant groups. These subgroups have therefore been combined for analysis.

RETROSPECTIVE REVIEW OF NEONATAL RECORDS

Neonatal records were reviewed for the results of screening for acute ROP and treatment by cryotherapy. Screening for acute ROP had been performed in individual neonatal units by local ophthalmologists who were masked to the randomisation group and treatment with surfactant. Pupil dilatation with phenylephrine 2.5% and cyclopentolate 0.5% was followed by indirect ophthalmoscopy generally using a speculum and indenter to rotate the eye. Findings were documented in accordance with the international classification of ROP⁹ – namely, stage 1: demarcation line; stage 2: ridge; stage 3: extraretinal fibrovascular proliferation; stage 4: partial retinal detachment; and stage 5: retinal detachment. Threshold disease was defined as at least 5 contiguous clock hours or 8 cumulative hours of stage 3 ROP in zone 1 or 2 in the presence of 'plus' disease (dilatation and tortuosity of the posterior retinal vessels).

EXAMINATION OF CHILDREN AT 2 YEARS

All neonates surviving until 2 years old were reviewed by one ophthalmologist who was masked to gestational age, neonatal events, whether the child had been allocated to the

prophylactic or rescue group, and the results of retrospective review of the notes.

Examination included visual acuity and cover test. Topical cyclopentolate 1% was instilled 20 minutes before refraction and funduscopy. Particular note was made of as much of the peripheral retina as possible and of the architecture of the posterior pole vessels to identify any minor tractional changes of cicatricial ROP. Additional information was gained from the child's notes when examination under anaesthetic had been performed.

Statistical analysis was by χ^2 , Fisher's exact test, and two sample *t* test.

Results

In the multicentre OSIRIS trial,⁸ prophylactic surfactant improved survival from 70% to 73.3% ($p=0.057$). There was also improved morbidity as shown by 32% fewer pneumothoraces (absolute difference -5.3% , 95% confidence interval -8.0% to -2.7%) and 22% fewer other pulmonary air leaks. The children in this study represent 184/2690 (6.8%) of the neonates in the OSIRIS trial. There was no significant difference between the two groups at randomisation (Table 1). The two groups showed the same trends of improved mortality and morbidity as the OSIRIS trial, although the smaller numbers make the results not statistically significant. Thus, survival until 2 years old was better in the group receiving prophylactic surfactant, with 102 of 151 (67.5%) surviving compared with 82 of 141 (58.2%, $p=0.17$, Table 2). There was a non-significant improvement in morbidity in those receiving prophylactic surfactant: the mean time on the ventilator was reduced from 17.8 days to 15.1 days ($p=0.31$) and there were fewer neonates with pneumothoraces requiring drainage (5.9% compared with 9.8%, $p=0.41$, Table 2).

One of the authors reviewed 181 of 184 survivors at approximately 2 years old. Cicatricial ROP occurred in 10 children, ranging from straightening of arcade vessels in association with high myopia to open funnel detachments (Table 3). The incidence of cicatricial ROP was lower in the group receiving prophylactic surfactant (4/100 survivors, 4.0%) compared with those receiving rescue surfactant as required (6/81 survivors, 7.4%) but this difference was not statistically significant ($p=0.35$). One patient with cicatricial ROP in each group had not received cryotherapy.

The survival and incidence of cicatricial ROP according to gestational age for the two

Table 1 Characteristics of neonates randomised to receive prophylactic surfactant compared with controls receiving rescue surfactant

	Prophylactic surfactant (n=151)	Rescue surfactant (n=141)	p Value
Gestational age (weeks)	27.18	27.31	0.55
Number (%) of males	86 (57.0)	88 (62.4)	0.40
Number (%) of neonates in multiple births	38 (25.2)	26 (18.4)	0.20
Number (%) receiving antenatal maternal dexamethasone	24 (15.9)	16 (11.3)	0.31
Number (%) of neonates with a pneumothorax requiring drainage	19 (12.6)	27 (19.1)	0.15
Number (%) born in teaching hospital	108 (71.5)	109 (77.3)	0.29

Table 2 Characteristics of surviving neonates randomised to receive prophylactic surfactant compared with controls receiving rescue surfactant

	Prophylactic surfactant	Rescue surfactant	p Value
Number surviving (%)	102 (67.5)	82 (58.2)	
Gestational age (weeks)	27.76	27.80	0.86
Number (%) of males	56 (54.9)	54 (65.9)	0.17
Number (%) of neonates in multiple births	26 (25.5)	14 (17.1)	0.21
Number (%) receiving antenatal maternal dexamethasone	17 (16.7)	11 (13.4)	0.68
Number (%) of neonates with a pneumothorax requiring drainage	6 (5.9)	8 (9.8)	0.41
Number (%) born in teaching hospital	75 (73.5)	66 (80.5)	0.30

Table 3 Main fundal abnormalities in ten 2-year-old children with cicatricial retinopathy of prematurity, according to gestational age at birth and treatment with cryotherapy

Gestational age (weeks)	Cryotherapy	Right fundus	Left fundus
A Prophylactic surfactant group			
23.0	NC	Peripheral RD+macular pigmentation	Traction+macular ectopia
23.7	R+L	Normal	Vessel traction
24.6	R+L	Normal	Traction+macular ectopia
27.3	R+L	Vessel traction	Vessel traction
B Rescue surfactant group			
24.4	NK	Vessel traction+tilted disc	Normal
24.7	R+L	Vessel traction+tilted disc	Tilted disc
25.0	R+L	Normal	Vessel traction
27.1	R+L	Vessel traction	Vessel traction
27.7	R+L	Subtotal RD including macula	Funnel RD
28.0	NC	Traction+macular ectopia	Traction+macular ectopia

NC=no cryotherapy as threshold not reached; R=right eye, L=left eye; NK=not known; RD=retinal detachment.

groups are shown in Figure 1. Of neonates born at 23 weeks' gestation receiving prophylactic surfactant, two out of the three survivors developed cicatricial ROP. No neonates born at 23 weeks' gestation survived in the group receiving rescue surfactant. However, despite increased survival in the group receiving prophylactic surfactant, there was no overall increase in the incidence of cicatricial ROP as there was a decreased incidence of cicatricial ROP in those over 23 weeks' gestation (prophylactic surfactant 2/97, 2.1%, rescue surfactant 6/81, 7.4%, not significant, $p=0.18$)

Unfortunately, screening for acute ROP was not comprehensive and no screening data could be found in the records of 40 neonates.

Figure 1 Deaths and 2 year survivors in children born at less than 30 weeks' gestation treated with (A) prophylactic or (B) rescue surfactant as required. Children developing cicatricial retinopathy of prematurity (ROP) are indicated according to gestational age at birth.

(These neonates consisted of 18 in the prophylactic and 22 in the rescue surfactant group. There was no statistically significant difference in the mean gestational age at birth of the neonates in these two groups: mean 28.44 and 28.40 weeks respectively, $p=0.91$.) The worst stage of acute ROP for the two groups is shown in Table 4. There was no significant difference between the two groups in the worst stage of acute ROP seen or in the number of screening examinations (prophylactic group 2.0 examinations/neonate screened and rescue group 2.1 examinations/neonate screened).

Discussion

Studies of ROP after rescue surfactant treatment for severe RDS compared with controls receiving no surfactant have been more difficult to interpret than studies of prophylactic surfactant. This is because historical controls¹⁰ or the use of neonates with less severe RDS as controls¹¹ are not necessarily comparable.

Previous studies of the effect of prophylactic surfactant on acute ROP have looked at small numbers but are consistent with this study.¹²⁻¹⁴ Holmes *et al* showed no effect of prophylactic surfactant on the incidence of ROP in 23 neonates compared with controls. Repka *et al* showed a decreased incidence of ROP after prophylactic surfactant compared with historical controls¹³ and no effect when contemporary controls were used.¹⁴ However, this latter study excluded the smallest babies who would be expected to have the highest incidence of ROP and therefore be the most likely to reveal any effect prophylactic surfactant may have had.

In our study, data from routine screening for acute ROP were not complete.¹⁵ This prevented proper statistical analysis but the data available are consistent with the results for cicatricial ROP. Thus, there was no significant difference between the two groups in the worst stage of acute ROP reached, with a trend for increased numbers without ROP in the prophylactic surfactant group. Bias

Table 4 Worst stage of acute retinopathy of prematurity (ROP) reached by neonates receiving prophylactic or rescue surfactant

Worst stage of acute ROP	Prophylactic surfactant group (number of neonates) (n=100)	Rescue surfactant group (number of neonates) (n=81)
Not screened	18	22
Stage 0	55	38
Stage 1	9	8
Stage 2	6	5
Stage 3	2	0
Stage 3 threshold	7	7
Unknown stage	3	1

towards increased identification of acute ROP in the rescue group owing to a longer hospital stay seems unlikely as there was no significant difference in the number of screening examinations in the two groups. Bias due to easier examinations in less sick neonates is possible but would tend to identify more ROP in the prophylactic surfactant group and reduce any possible protective effect of prophylactic surfactant on development of severe ROP.

This study has larger numbers than previous studies and is based on gestational age rather than birth weight, which has a closer correlation with the incidence of ROP.⁵⁻⁷ Nevertheless, the numbers with cicatricial ROP were not high enough to draw firm statistical conclusions. These results show a trend towards a reduction in gestational age-adjusted incidence of cicatricial ROP. If this trend is truly representative, then to have an 80% chance of demonstrating a significant difference ($p=0.05$) between the groups, it would have been necessary to examine 1400 children. The OSIRIS trial⁸ showed that prophylactic surfactant given to very premature neonates resulted in a 16% reduction in death or oxygen dependence at term ($p=0.001$) so such a study would be unethical. Thus, in the absence of further data, the following observations can be made which may offer some clues for future study.

The incidence of cicatricial ROP seems to be related to both gestational age and respiratory health of neonates. The survival of some neonates born at 23 weeks in the group receiving prophylactic surfactant was associated with a high incidence of cicatricial ROP (two of three survivors). As no babies born at 23 weeks survived in the rescue surfactant group, this is consistent with the hypothesis that ROP is related to gestational age and that factors improving survival increase the incidence of ROP.

The incidence of cicatricial ROP in all other children (born 24–29 weeks) was three times higher in the rescue surfactant group, although this did not reach statistical significance. This suggests that factors other than gestational age are important in the aetiology of ROP as prophylactic surfactant may protect against the development of severe ROP. Interestingly, the mechanism of this protection may be related to events occurring soon after birth. In the multicentre trial of prophylactic surfactant,⁸ 75% of neonates in the rescue surfactant group developed severe RDS and therefore received rescue surfactant at a mean of only 1 hour later than the prophylactic surfactant group (mean age of 180 minutes compared with 118 minutes).

The importance of early events in the pathogenesis of ROP is supported by Prendiville and Schulenburg⁵ who showed a significant correlation between the development of severe acute ROP (stage 3 and 4) and three independent factors (acidosis, partial pressure of arterial oxygen (P_{aO_2}) >12 kPa, and pneumothorax) occurring *before* the onset of the demarcation line. In contrast, there was no difference in the exposure to any of their 34 risk factors between

those neonates with mild (stage 1 and 2) and those with advanced (stage 3 and 4) acute ROP *after* the appearance of the demarcation line.⁵

Administration of natural surfactant results in a rapid increase in P_{aO_2} with marked hyperoxia occurring within 5 minutes.³ The increase in P_{aO_2} is less rapid after administration of synthetic surfactant¹⁶ such as Exosurf, but nevertheless there may be a period of instability with hyperoxia. All neonates in the rescue group who received surfactant had developed severe RDS. Therefore they would be expected to have had higher inspiratory oxygen requirements and ventilator pressures before surfactant treatment and greater fluctuations in P_{aO_2} as a result of surfactant administration. There was also a higher incidence of pulmonary air leaks/pneumothoraces in the rescue surfactant group which may result in further fluctuations in P_{aO_2} .

Flynn *et al*¹⁷ also noted that P_{aO_2} fluctuated over long periods in ventilated premature neonates despite transcutaneous oxygen monitoring and active control of inspired oxygen to avoid hyperoxia during study conditions. The time on the ventilator has been inversely related to the incidence of ROP.⁶ Premature neonates receiving prophylactic surfactant spent less time on the ventilator and this may be related to the effect of prophylactic surfactant on the incidence of cicatricial ROP.

In summary, although this study cannot draw any firm statistical conclusions it does suggest that improved survival does not necessarily result in an increased incidence of cicatricial ROP. Indeed, there may be further scope to improve the risk of ROP in very premature neonates by factors which affect respiratory health and physiological stability during the early neonatal period.

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