CURRENT TOPIC

Systematic review of prophylactic *vs* rescue surfactant

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Surfactant treatment has been shown by careful randomised trials to reduce the mortality and morbidity of very premature babies.[1] However, whether surfactant should be given as soon as the baby is born or withheld until the baby has respiratory distress syndrome (RDS) is controversial.

The objective of this review is to set out the reasons for and against giving surfactant at birth, present the clinical trial data available to date with a systematic review of those trials, and the conclusions that can be drawn from them.

"Prophylactic treatment" is defined as surfactant given down an endotracheal tube at initial resuscitation. "Rescue treatment" is when the surfactant given to an intubated baby several hours after birth when RDS has been diagnosed.

Reasons for prophylactic surfactant treatment

The lung epithelium of very premature babies is damaged within minutes of ventilation.[2] This causes protein to leak on to the surface and interferes with surfactant function.[3 4] Animal studies have shown that surfactant treatment, given as soon as possible after birth, reduces the severity of RDS and airway damage,[5] and improves blood gases, lung function, and survival.[6 7] Clinical trials have shown that surfactant treatment for very premature babies is very beneficial and remarkably safe.[1] For example, the Ten Centre Trial of ALEC[8] used prophylactically showed a 30% reduction in the incidence of RDS compared with control babies and a 48% reduction in neonatal mortality with no side effects.

It is impossible to know which baby will develop RDS and who, therefore, might benefit from surfactant treatment. The shorter the gestation the more likely the baby is to develop RDS, but older babies who are compromised in some way are also at risk of RDS and its complications. Normal neonatal practice is to anticipate and try to prevent problems. To wait until a baby requires ventilation and a high level of inspired oxygen[9] before giving a treatment which has now been shown to reduce the severity of RDS and save lives is counterintuitive.

Reasons for not giving surfactant at birth

If surfactant is given at birth some babies will be given surfactant unnecessarily.[10] It is expensive and should be used only when the babies need it. In the early days of surfactant treatment there was concern that surfactant might be harmful and it was decided, for some clinical trials, that it should be given only to babies who had severe RDS. There were also concerns that surfactant treatment at birth would interfere with resuscitation and destabilise the baby, and that if surfactant is administered without knowing the position of the endotracheal tube, it may be delivered into one area of the lung.[11] If surfactant treatment is equally effective when given a few hours after birth, the problems associated with early administration become irrelevant.

Selection of studies and criteria for analysis

A searched was made for all clinical randomised trials that compared surfactant treatment given at birth with that used to treat established RDS. They were obtained from a personal knowledge of published findings, a Medline search, information from research workers in this field and from the National Perinatal Epidemiology Unit. Ten appropriate published randomised clinical trials were found.[10–19]

The criteria for inclusion of trials in the analysis were: trials should have been appropriately randomised; the prophylactic surfactant had to have been given at initial resuscitation and certainly within minutes of birth; rescue surfactant should only have been given to infants ventilated infants for RDS.

Four trials were excluded from the analysis. They were:

The OSIRIS trial[16] because the early or prophylactic treatment was not given at birth. The median time for the first dose was 118 minutes. Merritt *et al*[17] because rescue treated babies were excluded if the tracheal aspirate had an L:S lecithin:sphingomyelin ratio of 2.0 or more with phosphatidyl glycerol present, even though they were ventilated in at least 50% oxygen. This did not happen to the prophylactically treated babies. Only babies with RDS were included in the final analysis.

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Table 1 Summary of data from randomised controlled trials

Author	*Surfactant*	*Entry criteria*	*Exclusions*	*Primary outcome*	*Sample size calculation*	*Number of centres*	*Control group*	*Blinded*	*Technique of randomisation*
Dunn[10]	Calf (now called BLES)	< 30 weeks	Malformations, rupture of membranes > 2 weeks and oligohydramnios	Difference in arterial, alveolar oxygen ratio of 0.1 (0.15)	60 per group at 90% power at α =0.05	1	Yes	No	Envelopes sequentially numbered. Randomisation not stated. Stratified 24-26 weeks and 27-29 weeks
Kendig[11]	Calf (now called Infasurf)	< 30 weeks	Malformations	15% difference in survival	450 total at 80% power and α =0.05	3	No	No	Envelopes consecutively numbered for each centre. Randomised blocks of 8
Egberts[12]	Curosurf	26-30 weeks	Malformations, ROM > 3 weeks	40% increase in transcutaneous oxygen to FiO_2 ratio, 50% reduction in *x* ray of RDS	50 per group for 1st outcome and 57 per group for second outcome at 80% power and α =0.05	4	No	No	Envelopes in each centre in blocks of 4 or 8
Kattwinkel [13]	Infasurf	29-32 weeks	Malformations, positive blood culture at birth. Judged too mature, severe perinatal asphyxia	7% difference in moderate RDS (mean airway pressure => 8 cm H_2O or FiO_2 =>0.4)	1320 total at 90% power and α =0.05	8	No	No	Envelopes. Randomisation not stated
Walti[14]	Curosurf	25-31 weeks	Malformations, stillborn, ROM > 3 weeks	20% difference in survival without BPD at 28 days	250 total at 90% power and α =0.05	12	No	No	Envelopes Randomisation not stated
Bevilacqua [15]	Curosurf	24-30 weeks	Malformations or infection	To reduce by 30% the incidence of grade 3-4 RDS	280 total at 80% power and α 5%	18	No	No	Envelopes stratified for gestation

Some babies, eligible on gestational age criteria, were not enrolled because the amniotic fluid analysis suggested they had mature surfactant. The problem was that not all fetuses were submitted to this analysis. Bevilacqua *et al*[18] was excluded because babies were enrolled in the study after two hours and the first dose was not given before this time. Babies were excluded from the study if their oxygen requirements at enrolment were less than 40% or more than 59%. Therefore, the mildly ill and sickest babies were not enrolled. Konishi *et al*[19] was excluded because gastric aspirate was collected after birth and tested before the decision was made to enrol the baby in the trial. Therefore, this was not prophylactic treatment.

The information about the entry criteria, exclusions, primary outcomes, sample size calculations, number of centres and techniques of randomisation are shown in tables 1 and 2. The basic demographic data for the enrolled babies are shown in table 3.

Analysis of the trials

The data were analysed using Cochrane Collaboration review manager software, Rev-Man, version 2.1a, 1995. This is designed to facilitate the preparation, production, and analysis of a systematic review and follows previously published techniques.[20] The results of the main outcomes are shown in fig 1.

The neonatal mortality was significantly reduced by prophylactic surfactant with an Odds Ratio (OR) and 95% confidence intervals (CI) of 0.55 (0.41 to 0.73) (table 4). This was a 39% reduction in the incidence of neonatal deaths from 139/1251 (11.1%) to 86/1269 (6.8%). The overall mortality by the

Table 2 Techniques and criteria for administering surfactant

Author	*Dose of surfactant*	*Technique of giving surfactant*	*Criteria for intubation prophylactic group*	*Time of prophylactic dose*	*Criteria for intubating babies in the rescue group*	*Criteria for giving surfactant to the rescue group*	*Criteria for additional doses for both groups*
Dunn[10]	25 mg/ml, 24-26 wk - 3 ml, 27-29 wk - 4 ml	Catheter down the endotracheal tube in 3 aliquots. Bag ventilation with each aliquot	Elective at birth	Before the first breath, breathing prevented before surfactant	Apnoea, needing oxygen, has RDS. Unit policy to ventilate all babies <30 weeks	All babies treated no later than 6 hours unless no evidence of RDS	Up to 3 doses in first 5 days, given if FIO_2 increase by 0.1 over lowest baseline
Kendig[11]	90 mg in 3 ml	Catheter down the endotracheal tube in 4 aliquots. Bag ventilation with each aliquot	Elective at birth	Within seconds of intubation	Not stated	If chest *x* ray shows RDS and FIO_2>0.4, mean airway pressure >7.0cm H_2O either or both. Hand ventilated before surfactant given	At intervals of 12 to 24 hours if FIO_2 >0.4, mean airway pressure >7 cm H_2O or both
Egberts[12]	200 mg/kg, 2.5 ml/kg	With a catheter down the endotracheal tube in one bolus	Elective at birth	Within 10 minutes	Intubated at birth	If ventilated and FIO_2 >0.6 at 6 to 24 hours	Second dose at 6 hours or rescue treatment if FIO_2 >0.6
Kattwinkel [13]	4.5 ml per dose, 150 mg per dose	Instilled into the trachea	Elective as soon as practical	By 5 minutes	Chest *x* ray showed RDS and $FIO_2 \geq 0.3$	Chest *x* ray shows RDS and FIO_2>0.3 and intubated. Given straight after intubation	Repeated if FIO_2>0.6 and MAP>10 cm H_2O
Walti[14]	100 mg/kg, 1.25 ml/kg	With a catheter down the endotracheal tube in 2 aliquots.	Elective at birth	By 15 minutes	If PaO_2 less than 6.6 kPa (50 mm Hg) with $FIO_2 \geq 0.3$ and/or $PaCO_2$ >7.3 kPa (55 mm Hg)	Chest *x* ray shows RDS and PaO_2/FIO_2 <150 mm Hg (20 kPa) at mean airway pressure of 8 cm H_2O	Up to 3 doses in 48 hours. If PaO_2/FIO_2 <150 mm Hg (20 kPa)
Bevilacqua [15]	200 mg/kg, 2.5 ml/kg	With a catheter down the endotracheal tube as a bolus	At birth on clinical grounds	By 10 minutes	According to the routine of each unit	Chest *x* ray shows RDS and needing ventilation irrespective of inspired oxygen	Up to 3 doses in 48 hours. If PaO_2/FIO_2 <150 mm Hg (20 kPa)

Table 3 Demographic data for babies enrolled in trial

	Number analysed		Number excluded after enrolment		Gestational age Mean (SD)		Birthweight Mean (SD)		Males		Antenatal steroids		Caesarean section	
	Prophylaxis	Rescue	Prophylaxis	Rescue	Prophylaxis	Rescue	Prophylaxis	Rescue	Prophylaxis	Rescue	Prophylaxis	Rescue	Prophylaxis	Rescue
Dunn[10]	62	60	0	0	26.9 (1.7)	27.2 (1.4)	962 (270)	986 (220)	45%	60%	47%	50%	53%	60%
Kendig[11]	235	244	0	0	27.5 (2.1)	27.5 (2.0)	1023 (323)	1040 (295)	55%	56%	28%	34%	60%	64%
Egberts[12]	75	72	1	1	28.0 (1.2)	27.8 (1.3)	1033 (237)	1126 (295)	55%	56%	25%	32%	60%	46%
Kattwinkel[13]	627	621	79	71	31.0 (1.3)	30.9 (1.3)	1599 (346)	1608 (350)	53%	54%	NR	NR	48%	49%
Walti[14]	134	122	14	18	28.9 (1.2)	28.3 (1.3)	1211 (289)	1150 (270)	56%	52%	17%	11%	58%	48%
Bevilacqua[15]	136	132	9	9	28.0* (24-30)	28.0* (24-30)	1010 (296)	1002 (310)	52%	47%	28%	28%	64%	66%

* Median and range.

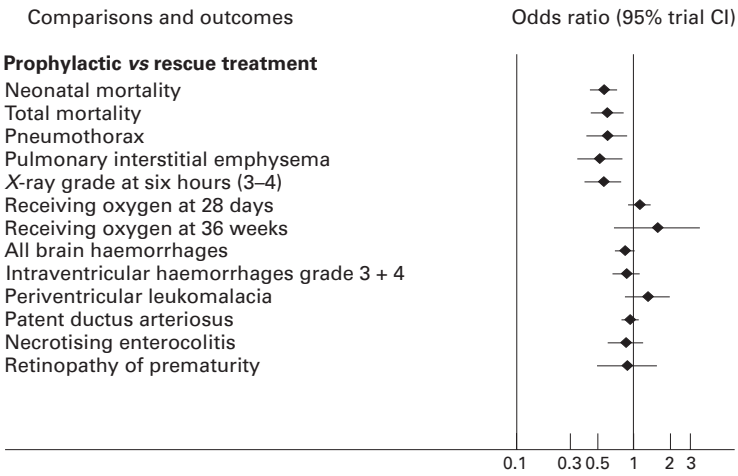

Figure 1 Comparison of outcomes with both types of treatment.

Table 4 Neonatal mortality

Trial	Prophylaxis	Rescue	Odds Ratio	95% CI low	95% CI High
Dunn[10]	9/62	8/60	1.82	0.60	5.54
Kendig[11]	23/235	40/244	0.56	0.33	0.95
Egberts[12]	8/75	14/72	0.50	0.20	1.24
Kattwinkel[13]	3/627	11/621	0.31	0.10	0.89
Walti[14]	15/134	23/122	0.54	0.27	1.08
Bevilacqua[15]	28/136	46/132	0.49	0.28	0.83
Totals	86/1269 (7%)	139/1251 (11%)	0.55	0.41	0.73

Table 5 Total mortality

Trial	Prophylaxis	Rescue	Odds Ratio	95% CI low	95% CI High
Dunn[10]	9/62	8/60	1.10	0.39	3.06
Kendig[11]	29/235	49/244	0.56	0.34	0.92
Egberts[12]	10/75	15/72	0.58	0.25	1.39
Walti[14]	18/134	29/122	0.50	0.26	0.94
Totals	66/506 (13%)	101/498 (20%)	0.59	0.42	0.82

Table 6 Pneumothorax

Trial	Prophylaxis	Rescue	Odds Ratio	95% CI low	95% CI High
Dunn[10]	3/62	5/60	0.56	0.13	2.36
Kendig[11]	16/235	29/244	0.55	0.29	1.01
Egberts[12]	2/75	5/72	0.39	0.08	1.77
Kattwinkel[13]	8/627	11/621	0.71	0.29	1.77
Walti[14]	3/130	6/121	0.46	0.12	1.75
Bevilacqua[15]	10/136	12/132	0.79	0.33	1.89
Totals	42/1265 (3%)	68/1250 (5%)	0.60	0.40	0.88

Table 7 Pulmonary interstitial emphysema

Trial	Prophylaxis	Rescue	Odds Ratio	95% CI low	95% CI High
Dunn[10]	2/62	5/60	0.39	0.08	1.79
Egberts[12]	2/75	5/72	0.39	0.08	1.77
Kattwinkel[13]	3/627	3/621	0.99	0.19	4.92
Walti[14]	16/131	24/121	0.56	0.28	1.11
Bevilacqua[15]	9/136	19/132	0.43	0.19	0.95
Totals	32/1031 (3%)	56/1006 (6%)	0.51	0.32	0.79

time of discharge was also significantly reduced with an OR and 95% CI of 0.59 (0.42 to 0.82) (table 5). However, this was only reported for the four trials with babies less than 32 weeks' gestation.[10–12 14] There was a 36% reduction in the incidence of total deaths from 101/498 (20.3%) to 66/506 (13.0%). This suggests that prophylactic surfactant would save about seven more lives than rescue treatment for every 100 babies treated.

The incidence of pneumothoraces was significantly reduced with an OR and 95% CI of 0.60 (0.40 to 0.88) (table 6). This is a 39% reduction in the incidence of pneumothoraces from 68/1250 (5.4%) to 42/1265 (3.3%).

The incidence of pulmonary interstitial emphysema was significantly reduced with an OR and 95% CI of 0.51 (0.32 to 0.79) (table 7). This is a 45% reduction in the incidence of pulmonary interstitial emphysema from 56/1006 (5.6%) to 32/1031 (3.1%).

The incidence of severe RDS graded from the chest *x* ray pictures[21] was only reported in three trials.[12 14 15] There was a significant reduction with an OR and 95% CI of 0.54 (0.38 to 0.77) (table 8).

There were no significant differences in the incidence of chronic lung disease, defined by a requirement for oxygen at 28 days of life or 36 weeks' gestation, brain haemorrhages, or periventricular leucomalacia, patent ductus arteriosus, necrotising enterocolitis or retinopathy of prematurity. However, there was a strong trend towards a reduction in brain haemorrhages.

EFFECT ON THE SEVERITY OF RDS

The trials all recorded different information about the influence of the two surfactant regimens on oxygenation, ventilation, and the severity of RDS. Therefore, it is not possible to compare these in a meta-analysis. However, all the trials showed improvements in gas exchange and the severity of RDS with the use of prophylactic surfactant. Dunn *et al*[10] showed significant improvement in gas exchange in the prophylactic group at 24 and 48 hours compared with the control group. Kendig *et al*[11] showed that the babies in the prophylaxis group had consistently lower requirements for supplemental oxygen and ventilatory assistance in the first 72 hours and less severe RDS. Egberts *et al*[12] showed that surfactant treatment at birth was associated with significantly better oxygenation at 6 hours, an improved $tcPO_2$:/FIO_2 ratio from 39.7 to 28.1 ($P < 0.001$), and a 41% improvement for the early treated group.

Table 8 X-ray grade (3 or 4) at six hours

Trial	*Prophylaxis*	*Rescue*	*Odds Ratio*	*95% CI low*	*95% CI High*
Egberts[12]	14/75	26/72	0.41	0.20	0.86
Walti[14]	18/128	23/119	0.64	0.33	1.26
Bevilacqua[15]	38/136	54/132	0.56	0.34	0.93
Totals	70/339 (21%)	104/323 (32%)	0.54	0.38	0.77

There was a lower incidence of severe RDS, 19% *vs* 36% (P <0.05) and a 36% reduction in the incidence of moderate to severe RDS. The prophylactically treated babies were receiving more than 40% oxygen (P <0.01) for a shorter time.

Kattwinkel *et al*[13] showed that prophylactic surfactant was associated with a lower incidence of moderate RDS—7% *vs* 12% (P = 0.004). This was mainly in the babies of less than 30 weeks' gestation—10% *vs* 23% (P = 0.021)—and a lower incidence of ventilation or supplemental oxygen trended over the first few days (P < 0.02), lower mean airway pressure over the first 48 hours for ventilated babies (P<0.03) and fewer babies needing supplemental oxygen at 28 days—5% *vs* 7% (P=0.071).

Walti *et al*[14] showed that within 3 to 72 hours of birth the prophylactic group had a higher pH, PaO_2:FIO_2 ratio, and a:A pO_2 ratio and lower FIO_2. They also had a lower respiratory rate, peak inspiratory pressure, and mean airway pressure. Bevilacqua *et al*[15] showed that the maximum FIO_2 during the first 28 days was lower in babies given prophylaxis than in controls.

There was no evidence from any of the trials that prophylactic surfactant had a deleterious effect at the time it was administered or subsequently.

The proportion of babies treated with surfactant in each group and the total number of doses given to each group are shown in tables 9 and 10. The babies treated prophylactically required about 70% more doses of surfactant than the rescue group. However, the babies in the rescue group who were treated with surfactant received an average of 1.5 doses compared with 1.2 in the prophylactic group.

Table 9 Percentage of babies in each group who received surfactant

Trial	*Prophylaxis*	*Rescue*
Dunn[10]	100	90
Kendig[11]	97	59
Egberts[12]	100	32
Kattwinkel[13]	100	43
Walti[14]	98	55
Bevilacqua[15]	100	40
Average % treated	99	48

Table 10 Total number of doses of surfactant given to each group

Trial	*Prophylaxis*	*Rescue*
Dunn[10]	112	81
Kendig[11]	322	248
Egberts[12]	83	23
Kattwinkel[13]	661	321
Walti[14]	234	161
Bevilacqua[15]	142	53
Doses per baby enrolled	1.2	0.7
Doses per baby treated	1.2	1.5

Cost and benefits of prophylactic surfactant

Survival is the most important outcome. The data on overall survival are available from four trials[10–13] and for babies less than 32 weeks' gestation (table 5). However, these are the group who are most at risk of dying and other serious complications. If 100 babies were treated prophylactically about 148 doses would be used, whereas if they received rescue treatment, about 100 doses would be used. Therefore, prophylactic treatment of 100 babies would require about 48 more doses than rescue treatment.

However, prophylactic treatment saves about seven extra lives for every 100 treated. Therefore, prophylactic surfactant would cost about seven more doses of surfactant for every extra life saved. The cost of surfactant for each extra life saved, for the different surfactants marketed in the UK in 1997, would be approximately: ALEC £1050 (£150 per phial), Exosurf and Survanta £2142 (£306 per phial), and Curosurf £2800 (£400 per phial).

There are other unmeasurable costs. The babies in the rescue group have more severe RDS and more pneumothoraces and this increases the cost of their care. As more babies survive in the prophylactically treated group the cost of their ongoing care would be greater.

Conclusions

Theoretical, animal, and clinical data now show that surfactant given at birth to babies of less than 32 weeks gestation improves survival and reduces complications. The data from this systematic review show a 39% reduction in the neonatal mortality if the babies are treated with surfactant at birth compared with a few hours later. The odds ratio of 0.55 in favour of prophylactic surfactant is very significant, and is similar to the effect of antenatal steroids where the odds ratio for neonatal mortality is 0.60. It is also similar to the effect of surfactant treatment, overall, where the reduction in neonatal mortality has an odds ratio of 0.55.[22]

The trials in this analysis used calf and porcine surfactant. It is likely, but unproved in randomised trials, that other surfactants would have a similar effect.

Systematic reviews cannot be definitive because they only assess the data available to the authors. In this review the trials are heterogeneous in the type of surfactant used, the dose and dosing regimen, the enrolment criteria and the number of patients. This makes comparison and meta-analysis difficult. However, such heterogeny lends weight to the significance of the main outcomes—reduction in the severity of RDS and increased survival.

Instilling relatively large amounts of fluid into the lungs of premature babies at birth may be difficult. However, those surfactants which use the lowest volumes will be easier to use and probably should be used in preference, although there are no comparative data. My own experience with the surfactant ALEC, at 1.2 ml per dose, is that administration at birth is easy and does not destabilise the baby.[23]

There are no data to suggest that prophylactic surfactant treatment causes any more problems than subsequent treatment. The only negative fact against universal prophylactic surfactant seems to be the cost of the extra surfactant. However, although more expensive, there is the considerable benefit of saving seven more babies for every 100 born at less than 32 weeks of gestation. It can be crudely calculated that for these babies the cost of surfactant for each extra survivor is the cost of seven doses. Compared with many treatments, and the total cost of caring for very premature babies, prophylactic surfactant is a relatively cheap way of improving neonatal survival.

The practical decision for neonatologists is which babies to treat prophylactically. The problem is that it is not possible to know immediately at birth which babies will develop RDS. Obviously, the lower the gestational age the more likely the baby is to develop serious RDS and its complications. However, more mature babies can develop severe RDS if they are compromised. The upper gestational age cutoff for prophylaxis is not easy to define because there are few satisfactory data. The data from these trials suggests that at less than 32 weeks of gestation prophylactic surfactant is beneficial. Pragmatically, my personal practice is to recommend that all babies less than 32 weeks gestation should be treated with surfactant as soon as they are intubated. This means that those who need resuscitation and ventilation from birth will be given surfactant at birth, and those who subsequently require ventilation will receive their surfactant when they are intubated.

The varied and almost arbitrary nature of the criteria in these trials about when to give rescue treatment and re-treat babies means that no guidance can be given about how soon to give rescue treatment and when to re-treat the sickest babies.

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