Early versus delayed neonatal administration of a synthetic surfactant — the judgment of OSIRIS

THE OSIRIS COLLABORATIVE GROUP
(OPEN STUDY OF INFANTS AT HIGH RISK OF OR WITH RESPIRATORY INSUFFICIENCY—THE ROLE OF SURFACTANT)

Although exogenous surfactants are of known efficacy in the prevention and treatment of respiratory distress syndrome (RDS), questions remain about the best regimens. During 1990–91, 6774 babies were recruited to an international multicentre trial to assess when administration of Exosurf, a synthetic surfactant, should be started and how often it should be given.

The clinical outcome is known for 6757 (99·7%) infants. 2690 babies, judged to be at high risk of RDS when less than 2 hours of age, were randomly allocated to either early administration or delayed selective administration; 96% versus 73% received surfactant, at median ages of 118 and 182 min. The risk of death or dependence on extra oxygen at the expected date of delivery was 16% (95% CI 25% to 7%) lower among infants allocated early administration. Early administration was also associated with a 32% lower risk of pneumothorax. These 2690 infants were further randomised in a factorial design to either two doses of surfactant 12 hours apart, or the option of third and fourth doses at 12–36 hour intervals if signs of RDS persisted or recurred. 4067 other infants who later developed RDS were also recruited to this comparison, giving a total of 3376 infants allocated up-to-four doses (of whom, 45% received more than two) and 3381 allocated two doses. The outcome was similar in the two groups in respect of death, long-term oxygen dependence, and other major morbidity, even in secondary analyses restricted to infants who met the criteria for additional administration. There were more reports of poorly tolerated administration in the up-to-four doses group but no clear increase in serious morbidity, such as pulmonary haemorrhage.

The OSIRIS trial suggests that early administration of surfactant to an estimated 32 babies, when compared with treatment of established RDS, would prevent 1 baby from dying and another from being dependent on extra oxygen long-term, but would entail the additional use of surfactant in 8 of these babies. It provides no evidence that a regimen including the option of third and fourth doses when signs of RDS persist or recur is clinically superior to a regimen of two doses.

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Patients and methods

Early versus delayed selective administration comparison

Infants were eligible for the early versus delayed selective administration comparison if: (1) the risk of RDS was judged by the clinician responsible for care to be sufficiently high to consider immediate administration of surfactant; (2) the age was less than 2 hours; (3) endotracheal intubation was required for respiratory assistance; (4) there was no contraindication, such as a major malformation; and (5) there was no parental objection to the baby's participation. After entry, these infants were randomly assigned to either early administration of surfactant as soon as possible, or delayed selective administration. Infants randomised to delayed selective administration were to receive surfactant if they met the following criteria: (1) the baby was more than 2 hours old; (2) endotracheal intubation was required for respiratory assistance; (3) a clinical diagnosis of RDS had been made; and (4) the arterial/alveolar oxygen partial pressure (a/A) ratio[3] was less than 0·22. No infant was to be intubated for the sole purpose of surfactant administration.

Dosing comparison

Infants considered soon after birth to be at high risk of RDS were further randomised in a factorial design to either two doses of Exosurf 12 hours apart, or two doses of Exosurf 12 hours apart with the option to give up to two further doses of Exosurf at intervals of about 12 hours if the criteria for selective administration for RDS persisted or recurred. These third and fourth doses could, exceptionally, be given up to 24 hours after they were first due if the baby's condition improved then deteriorated. Other infants who later (2–72 hours of age) fulfilled criteria for selective administration of surfactant for RDS were also recruited to this dosing comparison.

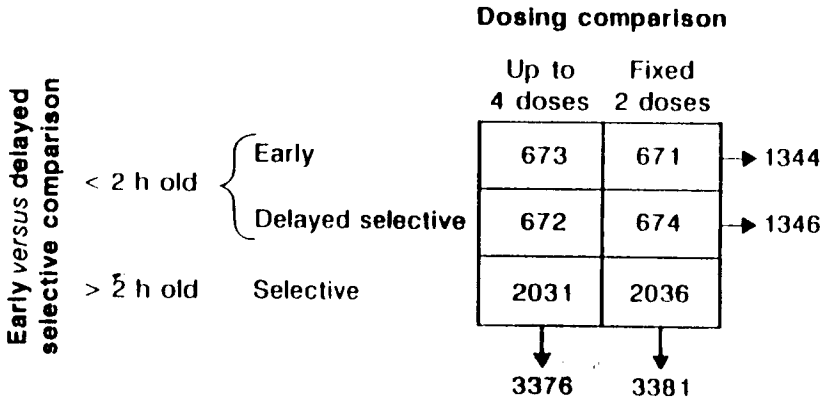
The prespecified primary measures of outcome were: (1) death or dependence on supplemental oxygen at 28 days of age; (2) death at any time; and (3) prolonged oxygen dependence, defined as the persisting need for daily supplemental oxygen on the "expected date of delivery"

Statistical methods

It was precalculated that at least 2000 babies would have to be recruited to the early versus delayed selective comparison to be about 80% confident of identifying a major additional benefit (in any of the three principal measures of outcome) at a 5% level of statistical significance, for 1 baby out of every 20 treated early (that is, a 5% absolute difference), assuming the rate of this outcome was about 25%. The aim, however, was for a larger sample size in the hope of identifying a smaller, 1 in 30 additional benefit (3·3% absolute difference) because discussions had indicated that this was also considered clinically important. A substantially larger sample size was required for the dosing comparison (on the assumptions of 80% power and 5% level of statistical significance and a 1 in 30 benefit) because only 50% of babies in the group randomised to receive up-to-four doses if clinical signs persisted were expected to receive more than two doses. The babies in this part of the trial were also expected to be at lower risk of death and long-term dependence on extra oxygen.

All primary analyses were based on the groups as randomly allocated (intention-to-treat)

. Results are presented as rate differences and relative risks (with 95% CI), and means or medians where appropriate.



Derivation of study groups.

Results

Outcome information is available for 6757 (99·7%) of the 6774 infants recruited to the trial. The derivation of the study groups compared in this report is shown in the figure; 2690 babies were deemed to be at high risk of RDS when aged less than 2 hours and were recruited to the comparison of early administration (N = 1344) with delayed selective administration (N = 1346). All 6757 babies were assigned to one or other policy for dosing: 3376 to up-to-four doses and 3381 to two doses.

Early versus delayed selective administration comparison

The groups generated by random allocation to either early administration or delayed selective administration were broadly similar at trial entry, although there was a slight, non-significant, imbalance in the use of antenatal corticosteroids (table I); overall, 45% were less than 28 weeks' gestation and 39% were less than an hour old at the time of recruitment. 96% of those allocated early administration actually received surfactant, compared with 73% allocated the delayed selective policy (table II). Among those who actually received surfactant, treatment was started sooner in the group allocated to early administration (median age at first administration 118 minutes versus 182 minutes). Overall, the early administration group received about 1½ times more exogenous surfactant. This extra use of surfactant was associated with more reports of poorly tolerated administration and endotracheal tube problems, including blockage, but these differences were not statistically significant (table II).

[illegible]come for babies allocated early administration was better than that of babies allocated delayed selective administration in respect of all three principal measures of outcome (table III). The greatest difference was seen on the expected date of delivery. At that time, the risk of oxygen dependence or death was reduced by a factor of 16% (95% CI 25% to 7%). The absolute difference was −6·3% (95% CI − 9·9% to −2·7%); early administration to an estimated 16 babies would therefore prevent 1 baby dying or being long-term dependent on oxygen. Table IV shows that this reflects beneficial effects on both the risk of death and the risk of long-term oxygen dependence, of about equal size.

These differences in the principal measures of outcome were reflected in the group allocated early treatment being more likely to survive and be extubated by one month of age (64% versus 59%), to survive and be in <40% oxygen at 3 months (71% versus 67%), to survive and be breathing air at 3 months (66% versus 60%), and to have been discharged from hospital at 3 months (58% versus 52%).

TABLE I—COMPARABILITY OF GROUPS AT TRIAL ENTRY

—	Early *vs* delayed selective comparison		Dosing comparison	
	Early (n = 1344)	Delayed selective (n = 1346)	Up to 4 doses (n = 3376)	Fixed 2 doses (n = 3381)
*Multiples % (no)	22·7 (305)	21·8 (293)	22·6 (764)	22·4 (758)
*Males % (no)	55·5 (746)	55·4 (746)	58·7 (1981)	58·9 (1991)
*Gestational age mean wk [SD]	27·86 [2·31]	27·87 [2·38]	29·56 [3·16]	29·56 [3·22]
<28, % (no)	45·5 (611)	44·5 (599)	27·5 (930)	27·5 (930)
<30, % (no)	78·0 (1048)	77·4 (1042)	52·0 (1754)	52·3 (1768)
Birthweight g mean [SD]	1121 [357]	1122 [384]	1411 [595]	1415 [607]
Antenatal corticosteroids % (no)†	23·3 (307)	20·7 (275)	15·5 (516)	15·5 (517)
Prolonged rupture of membranes % (no)§	22·4 (298)	22·8 (303)	17·6 (587)	16·7 (559)
Outborn % (no)	9·6 (129)	9·9 (133)	28·0 (944)	28·9 (976)
Mode delivery % (no)¶				
Vaginal	48·3 (645)	49·6 (664)	45·1 (1512)	46·3 (1556)
Prelabour caesarean	32·2 (430)	31·7 (424)	36·6 (1228)	35·4 (1191)
In labour caesarean	19·5 (261)	18·7 (250)	18·3 (614)	18·2 (613)
*Heart rate < 100 at 5 min % (no)	16·8 (226)	17·0 (228)	14·8 (499)	14·7 (497)
Age at entry—min‡				
Median {IQR}	69 {45,96}	71 {45,100}	221 {83,679}	230 {87,724}
<60% (no)	39·1 (514)	37·9 (496)	15·3 (504)	15·3 (506)

IQR = interquartile range. * = minimisation factor; †N = 1316,1330 and 3330,3325; §N = 1330,1329 and 3330,3338; ¶N = 1336,1338 and 3354,3360; ‡N = 1314,1309 and 3300,3306.

TABLE II—SURFACTANT ADMINISTRATION

—	Early *vs* delayed selective comparison		Dosing comparison	
	Early (n = 1344) % (no)	Delayed selective (n = 1346) % (no)	Up to 4 doses (n = 3376) % (no)	Fixed 2 doses (n = 3381) % (no)
Doses administered				
0	3·9 (52)	26·8 (361)	8·3 (280)	7·1 (240)
1	13·5 (182)	10·7 (144)	11·1 (374)	9·4 (318)
2	61·5 (827)	45·2 (608)	35·1 (1186)	82·8 (2801)
3	7·1 (95)	5·4 (73)	14·5 (488)	0·3 (10)
⩾4	14·0 (188)	11·9 (160)	31·0 (1046)	0·2 (7)
Not known	0	0	0·1 (2)	0·1 (5)
Administration problems				
Poorly tolerated	6·8 (91)	5·1 (69)	6·7 (226)	4·2 (142)
Tube problem	1·2 (16)	0·7 (9)	1·2 (40)	0·9 (31)
Age at first administration—min				
Median {IQR}†	118·0 {90,153}	182·0 {132,276}	335·0 {164,792}	345·0 {165,826}

IQR = Interquartile range.
†N = 1278,977 and 3080,3123.

TABLE III—PRINCIPAL MEASURES OF OUTCOME

Principal outcome	Early (n = 1344) % (no)	Delayed selective (n = 1346) % (no)	Relative risk (95% CI)	% difference (95% CI)	p	Up to 4 doses (n = 3376) % (no)	Fixed 2 doses (n = 3381) % (no)	Relative risk (95% CI)	% difference (95% CI)	p
Death or oxygen dependence at 28 days	58·0 (779)	62·0 (834)	0·94 (0·88 to 1·00)	−4·0 (−7·7 to −0·3)	0·034	49·1 (1656)	48·5 (1641)	1·01 (0·96 to 1·06)	+0·5 (−1·9 to +2·9)	0·67
Known death	26·7 (359)	30·0 (404)	0·89 (0·79 to 1·00)	−3·3 (−6·7 to +0·1)	0·057	23·4 (790)	23·6 (797)	0·99 (0·91 to 1·08)	−0·2 (−2·2 to +1·9)	0·86
Death or oxygen dependence at "expected date of delivery"	31·9 (429)	38·2 (514)	0·84 (0·75 to 0·93)	−6·3 (−9·9 to −2·7)	0·001	29·7 (1004)	29·8 (1007)	1·00 (0·93 to 1·07)	−0·04 (−2·2 to +2·1)	0·97

Dosing comparison

The babies recruited to the dosing comparison were on average 12 days more mature, about 300 g heavier, and about 160 minutes older than those who only participated in the comparison of early and delayed selective administration. This reflected the fact that 60% of babies in the dosing comparison were recruited when over 2 hours of age after signs of RDS had developed. The groups generated by random assignment were very similar in all known respects (fourth and fifth columns of table I). Similar numbers in the two groups received no surfactant (8·3% and 7·2%; table II). Most of these (69%) were babies recruited within 2 hours of birth who were allocated delayed selective administration and therefore would not have received surfactant unless they met the criteria for administration. The median time of the first administration was about 5¾ hours, but with a wide range. Overall, 1528 (45·4%) in the up-to-four dose group compared with 17 (0·5%) in the fixed two-dose group received a third dose; and 1042 (31·0%), compared with 7 (0·2%), received a fourth dose (table II). This is equivalent to 72 extra doses for every 100 babies randomised. The extra use of surfactant in the up-to-four doses group was associated with 60% more reports of poorly tolerated administration (absolute difference +2·5%; 95% CI +1·4% to +3·6%), but no clear difference in the number of reports of endotracheal tube problems (table II).

The outcome was similar in the two groups in respect of all principal measures of outcome (tables III and IV) and in respect of all secondary measures of outcome (table V). Judged on the pre-specified secondary analyses, this was true irrespective of the type of baby treated and time of starting treatment. There was also no clear evidence that the extra use of surfactant in the up-to-four doses group increased the risk of pulmonary haemorrhage or pneumonia (table IV).

TABLE IV—MORTALITY AND OXYGEN DEPENDENCE

	Early *vs* delayed selective comparison		Dosing comparison	
	Early (n = 1344) % (no)	Delayed selective (n = 1346) % (no)	Up to 4 doses (n = 3376) % (no)	Fixed 2 doses (n = 3381) % (no)
Status at 28 days				
Dead	22·0 (296)	25·0 (337)	19·7 (665)	19·6 (663)
O_2 dependent	35·9 (483)	36·9 (497)	29·4 (991)	28·9 (978)
Not O_2 dependent	40·6 (546)	36·0 (484)	49·4 (1669)	50·0 (1691)
Not known	1·4 (19)	2·1 (28)	1·5 (51)	1·4 (49)
Mortality				
Deaths before discharge	26·3 (354)	29·6 (398)	23·0 (778)	23·4 (792)
Deaths after discharge	0·4 (5)	0·4 (6)	0·4 (12)	0·1 (5)
Status at "expected date of delivery"				
Dead	24·0 (323)	27·0 (363)	21·0 (708)	20·9 (705)
O_2 dependent	7·9 (106)	11·2 (151)	8·8 (296)	8·9 (302)
Not O_2 dependent	65·3 (878)	57·9 (780)	67·7 (2284)	67·4 (2279)
Not known	2·8 (37)	3·9 (52)	2·6 (88)	2·8 (95)