

Mortality, Severe Respiratory Distress Syndrome, and Chronic Lung Disease of the Newborn Are Reduced More After Prophylactic Than After Therapeutic Administration of the Surfactant Curosurf

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ABSTRACT. *Objective.* To test the hypothesis that prophylactic treatment with the surfactant Curosurf (Chiesi Farmaceutici SPA, Parma, Italy) improves survival and respiratory problems more than rescue treatment.

Design. Meta-analysis of three prophylaxis versus rescue treatment trials, conducted in four countries.

Methods. A meta-analysis was performed with the original, individual data of mortality, severe respiratory distress syndrome, and chronic lung disease of 671 newborns as outcomes. The random-effects logistic model (accounting for the trial-within-country structure) was applied and adjusted for imbalances in covariates.

Results. The probability of each outcome differed between the countries, but the actual treatment effect itself did not. The adjusted odds ratios (ORs) and confidence intervals (CIs) for prophylaxis versus rescue were as follows: mortality: OR, .47; 95% CI, .30 to .73; severe RDS: OR, .50; 95% CI, .33 to .74; and chronic lung disease of the newborn in the survivors at day 28 after birth: OR, .54; 95% CI, .34 to .86. Gender, birth weight, gestational age, and prenatal administration of glucocorticosteroids were significant confounding covariates.

Conclusion. The analysis shows that for the porcine surfactant Curosurf, prophylactic administration of surfactant has significant advantages over rescue therapy. *Pediatrics* 1997;100(1). URL: <http://www.pediatrics.org/cgi/content/full/100/1/e4>; mortality; respiratory distress syndrome; chronic lung disease of the newborn; surfactant, prophylaxis, meta-analysis.

ABBREVIATIONS. OR, odds ratio; CI, confidence interval; RDS, respiratory distress syndrome; CLDN, chronic lung disease of the newborn; BPD, bronchopulmonary dysplasia; RRR, relative reduction of the risk ratio; BW, birth weight.

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Meta-analyses have shown that prophylactic and rescue treatment with surfactant reduce mortality rate, severity of acute respiratory problems, and the incidence of chronic lung disease in preterm newborns.¹⁻³ After performing a meta-analysis of seven randomized trials comparing prophylaxis with rescue treatment,⁴⁻¹⁰ we found that prophylactic treatment reduced the mortality rate more than rescue treatment [odds ratio (OR), .65; 95% confidence interval (CI), .50 to .84]. Mortality rate is likely to be reduced because of less severe acute respiratory problems such as respiratory distress syndrome (RDS), pneumothorax and pulmonary interstitial emphysema. Furthermore, one might expect that if the acute respiratory problems are reduced, and if the number of patients per randomized group is large enough, the incidence of chronic lung disease of the newborn (CLDN) would also be lowered significantly. Even within these seven trials including more than 2700 preterm newborns this was not so (OR, .85; 95% CI, .67 to 1.06). Four different natural surfactants, and seven different protocols for treatment in at least eight different countries were used in these trials.⁴⁻¹⁰

In any meta-analysis of published results, heterogeneity among trials, possibly induced by differences among centers, populations, treatment protocols, surfactants, and so forth, can lead to both under- and overestimation of the magnitude of treatment effects as well as their statistical significance.¹¹ However, when individual data instead of general effect measures are available, the application of multivariate random-effect regression models can adjust for some variations in treatment effect that might have resulted from interstudy differences. In this study, using the data on the individual infants, we calculated the average effect among these trials (condensed in the term country) with respect to the outcomes: mortality, severe RDS, and CLDN, after different prophylactic or rescue treatment protocols with Curosurf in 34 neonatal intensive care units.

MATERIALS AND METHODS

Curosurf (Chiesi Farmaceutici SPA, Parma, Italy) is isolated from porcine lungs and its characteristics, clinical efficacy, and how and when it was given and tolerated have been described extensively.¹² The trials were performed during 1989 to 1991 in two Dutch and two Swedish neonatal intensive care units, during 1990 and 1991 in 12 French units, and during 1991 to 1992 in 18 Italian hospitals. The protocols of these trials have been described

TABLE 1. Summarized Treatment Protocols per Trial

Trial	Dutch-Swedish	French	Italian
PROPHYLAXIS:	n = 75 (42–33)	n = 134	n = 136
Time after birth	<10 minutes	<15 minutes	<10 minutes
Dose (mg/kg BW)	200	100	200
Retreatment if	RDS, IPPV* and $FiO_2^* \geq 0.6$	$PaO_2/FiO_2 < 20$ kPa at MAP* = 8 cm H ₂ O	RDS and IPPV, irrespective of the FiO_2
Retreatment at	6–24 hours	6 hours after first dose, and thereafter at 12 hours intervals	within 24 hours
Maximal total dose (mg/kg BW)	400 (2 × 200)	400 (4 × 100)	400 (2 × 200)
RESCUE:	n = 72 (39–33)	n = 122	n = 132
Intubation at birth	yes	no	no
Time after birth	6–24 hours and $FiO_2 \geq 0.6$	RDS and IPPV at 3–18 hours and $PaO_2/FiO_2 < 20$ kPa at MAP = 8 cm H ₂ O	RDS and IPPV within 24 hours and irrespective of the FiO_2
Dose (mg/kg BW)	200	100	200
Retreatment if	no	$PaO_2/FiO_2 < 20$ kPa at MAP = 8 cm H ₂ O	no
Retreatment	no	6 hours after first dose, and thereafter at 12 hours intervals	no
Maximal total dose (mg/kg BW)	200	400	200

* BW, birth weight; RDS, respiratory distress syndrome; IPPV, intermittent positive pressure ventilation; FiO_2 , fraction of inspired oxygen; MAP, mean arterial pressure.

elsewhere^{8–10}; the treatment schedules are summarized in Table 1. Different patient data books and databases were used in the three trials. Fields of interest for this study were merged from each database and edited, if necessary. The data of each trial within the new database were checked for errors by the respective trial coordinators.

Patients

The combined trials included 345 prophylactically treated infants and 326 enrolled infants, who were eligible for rescue therapy if they fulfilled the entry criteria for surfactant administration. A total of 57 infants were excluded from the trials because of violation of the entry criteria or withdrawal of parental consent (32 in France, 19 in Italy, 1 in The Netherlands, and 1 in Sweden). Table 2 shows the baseline characteristics of the treatment groups by country.

The Outcome Variables

In this study, analyses were performed to determine whether or not prophylaxis when compared with rescue treatment would result in lower incidence of the outcome variables. 1) Severe RDS was defined as grade 3 to 4 according to Giedion et al¹³ or Bomsel (see footnote at the bottom of this page)¹⁴; 2) Neonatal mortality, without a differentiation between respiratory and nonrespiratory causes; and 3) CLDN at 28 days after birth in the surviving infants. CLDN was defined as requirement for respiratory support (need for supplementary oxygen and/or ventilatory support). These outcome variables differ slightly from the primary endpoints of the three trials: 1) an improvement of the PaO_2/FiO_2 ratio⁸; a reduction of (severe) RDS^{8,10}; and 3) an increase of survival without BPD at 28 days after birth.⁹ In the three trials more infants were included than needed to detect assumed differences between the treatment protocols at an α error of 5% and a power (1- β) of 80 or 90%.

Statistical Methodology

Because for this meta-analysis we had access to the individual data rather than the overall effect estimates, the analyses amount to the usual multivariate regression models in which the proba-

bility of a specific outcome is modeled as a function of the treatment (randomly allocated) and several covariates. However, the usual logistic regression model is not applicable because the different trials were carried out in different countries under different circumstances. This stratification induces a correlation structure on the individual data and thus a random effects model was chosen in which all observations were stratified by country. We included the variable country in our models to account for additional variation attributable to country beyond, and not instead of that induced by the centers themselves. All *P* values are based on the appropriate likelihood ratio tests comparing a model with and without the treatment factor, but incorporating the random effect term and the covariates of importance: birth weight (BW), gestational age, gender, and prenatal administration of glucocorticosteroids.

As an initial analysis and for display purposes, we used a Mantel-Haenszel approach, showing the relation between treatment and outcome in a series of 2 × 2 tables, stratified by country. For a series of randomized trials the ORs obtained in this way will be very close to those obtained by logistic regression; the *P* values, however, are solely based on the logistic random-effects models. For the calculation of the adjusted ORs, the significant covariates were included in this model as regression terms. The software used was EGRET (“Epidemiological Graphics, Estimation, and Testing package, Analysis Module: PECAN”; SERC, Seattle, WA).

RESULTS

Baseline Characteristics

Table 2 shows the perinatal baseline characteristics of each trial. Treatment arms are well balanced in all but two cases: BW for the Dutch trial and gestational age for the French one. In view of the number of covariates and trials, this is well within bounds induced by chance fluctuations. Although both gestational age and BW in themselves are predictors for the outcomes under study, there was no measurable confounding effect attributable to these imbalances.

The necessity of stratification is clear from the differences among the trials with respect to the criteria of surfactant treatment and retreatment (Tables 1 and 3). The prophylactic administration of Curosurf occurred in all cases within 15 minutes. Rescue treatment was given independently of postnatal age in the French and Italian trials, whereas in the Dutch-

(Definition of the radiological stages of RDS according to Giedion et al¹³ and Bomsel¹⁴ are comparable: Stage I: very fine reticulo-granular pattern, normal lucency, air bronchogram within cardiac border. Stage II: generalized typical reticulo-granular pattern, slightly diminished lucency, air bronchogram extending the cardiac border. Stage III: confluent reticulo-granular densities, marked reduction of lucency with indistinct cardiac border. Stage IV: total opacification, white lungs).

TABLE 2. Perinatal Baseline Characteristics per Country and per Treatment Group

	The Netherlands		Sweden		France		Italy		Combined Trials	
	Prophylaxis	Rescue Treatment	Prophylaxis	Rescue Treatment	Prophylaxis	Rescue Treatment	Prophylaxis	Rescue Treatment	Prophylaxis	Rescue Treatment
Infants (n)	42	39	33	33	134	122	136	132	345	326
Gestational age (wks)	28.3 (1.3)	28.1 (1.2)	27.6 (1.1)	27.5 (1.3)	28.9 (1.2)	28.3 (1.3)*	27.5 (1.8)	27.4 (1.9)	28.3 (1.7)	28.0 (1.7)
Birth weight (g)	995 (219)	1133 (275)*	1082 (254)	1117 (321)	1211 (289)	1150 (296)	1010 (296)	1002 (310)	1093 (296)	1084 (299)
Male/female	23/19	19/20	18/15	21/12	75/59	63/59	71/65	62/70	187/158	165/161
Multiple birth	20	14	8	6	43	39	35	24	106	83
Vaginal/caesarean	25/17	24/15	13/20	15/18	56/78	65/57	49/87	45/87	135/210	149/177
Preeclampsia	8	6	7	7	18	8	14	10	47	31
Premature rupture of the membranes	5	13	7	7	30	35	28	26	70	81
Glucocorticoids	18	18	1	5	23	13	29	23	71	59
Tocolysis	22	25	11	12	69	66	33	32	135	135
Apgar 1 min ≤6	31	30	18	20	80	79	106	110	237	239
Apgar 5 min ≤6	8	9	17	16	24	18	75	80	138	134

* $P < 0.05$, means (standard deviations).

Swedish trial it was postponed for 6 hours postnatally. Rescue treatment was given after a median period of 6 hours in the Dutch and Swedish subgroups, and after 4 hours in the French study and 7 hours in the Italian study. Retreatment after prophylaxis occurred in 12% (Dutch), 9% (Swedish), 4% (Italian), and in 45% of the (French) infants. Rescue treatment was given to 31% (Dutch), 30% (Swedish), 40% (Italian), and to 55% (French), respectively, of the infants. Retreatment of rescue-treated infants was also allowed in the French study and it was done in 70% of these infants.

The Outcomes

The different trials, carried out in different countries under different circumstances and different groups of patients showed correlations between the individual observations attributable to the patient-within-country structure. This random effects term in the models for the three outcomes was highly significant (mortality, $P = .005$; severe RDS, $P = .05$; and CLDN, $P = .001$). Thus, the ORs for the outcomes of the combined results were corrected for the random effects term although this had virtually no effect on the estimates of the ORs. Table 4 summarizes in a series of 2×2 tables the relation of treatment and outcomes by country and for the combined trials, after correction for the random effects term.

Outcome 1: Reduction of RDS at Six Hours After Birth

The incidence of radiologically and/or clinically diagnosed very mild to severe RDS was 70.2% (grade 1 to 4) in the rescue-eligible groups and 64.2% in the prophylactically treated infants (relative reduction or risk ratio (RRR) 8.5%, not significant). For severe RDS (grade 3 to 4), it was 29.7% in the rescue-eligible group and 18.9% in the prophylactically treated infants (RRR, 36.4%; OR, .55; 95% CI, .38 to .79; $P = .001$). The incidence of the respiratory complications pneumothorax plus pulmonary interstitial emphysema was 20.6% in the rescue-eligible group and 12.2% in the prophylactically treated infants (RRR, 40.8%; OR, .54; 95% CI, .35 to .82).

The test for homogeneity of the four ORs for severe RDS was not significant suggesting that the differences in treatment effect between the trials (countries) can be explained by chance fluctuations.

Outcome 2: Reduction of Neonatal Mortality

Mortality was reduced in all three trials (resulting in an increased percentage of survivors) when comparing prophylaxis (84.9%) with rescue treatment (74.5%) (RRR on mortality, 40.7%; OR, .52; 95% CI, .35 to .76; $P < .001$). Again differences in estimated ORs can be attributed to chance fluctuations.

Outcome 3: Reduction of the Incidence of CLDN in Survivors at 28 Days After Birth

The incidence of CLDN at 28 days after birth was not reduced if all randomized infants were included in the calculation ($P = .15$). In the group of prophylactically treated survivors the incidence of CLDN at day 28 (24.4%) was reduced significantly when compared with the survivors of the rescue-eligible group

TABLE 3. Treatment of the Randomized Groups per Country

	The Netherlands		Sweden		France		Italy	
	Prophylaxis Trial Group (n = 42)	Rescue Trial Group (n = 39)	Prophylaxis Trial Group (n = 33)	Rescue Trial Group (n = 33)	Prophylaxis Trial Group (n = 134)	Rescue Trial Group (n = 122)	Prophylaxis Trial Group (n = 136)	Rescue Trial Group (n = 132)
Treated infants	42	13	33	10	131	67	136	53
Retreated	5	—	3	—	59	47	6	—
mg Curosurf/treated infant	220	200	220	200	180	240	210	200
Dose 1* (min; h)	<10 min	6 h [6–10 h]	<10 min	6 h [6–24 h]	<15 min	4 h [1–19 h]	2 min	6 h [1–24 h]
Dose 2 (h)	6 h [6–12 h]	—	7 h [6–24 h]	—	6 h [3–42]	12 h [7–38 h]	7 h [4–16 h]	—

* Dose was 100 mg/kg in the French trial and 200 mg/kg in the Dutch-Swedish and Italian trials. The postnatal age in hours for surfactant administrations are given as medians and ranges.

(31.7%) (RRR, 23%; OR, .67; 95% CI, .45 to 1.00; $P = .05$). Although significant changes were not found between the separate trials and differences in estimated ORs are most likely the result of chance fluctuations, heterogeneity might be present.

Evaluation of Possible Confounding Covariates

The usual logistic model probably yields P values that are too optimistic because that model assumes all individual observations to be independent, which is not true. The variable country, which includes differences in rescue and normal-procedure protocols and also in populations, was a significant random effects term that therefore needs to be taken into account when calculating the significance (P value) of any treatment effect. This was done by incorporating it as a stratification variable in a random effects logistic model.

Independent of the effect of prophylaxis, we found that male neonates were more likely to develop severe RDS than female neonates ($P < .001$), that the rate of severe RDS decreased significantly in neonates with higher BWs or gestational ages, and if corticosteroids were given prenatally. The same variables as for RDS will change the OR values of mortality, and except for an effect of corticosteroids, also those of CLDN. Multiple birth, preeclampsia, and caesarean section were insignificant covariates. The ORs for these outcomes, and adjusted confounding covariates are shown in Table 4.

DISCUSSION

The mortality rate and the incidence of RDS and CLDN in survivors decrease after the prophylactic and therapeutic administration of surfactant,^{1–3} but lower odds for CLDN were only observed if the meta-analyses were limited to surviving infants.⁴ Both strategies for surfactant therapy have their advantages and disadvantages and trials were started, comparing the effects of the prophylactic and therapeutic approach. Meta-analysis of the seven studies,^{4–10} comparing prophylaxis with rescue therapy in very premature neonates shows that prophylaxis reduced the mortality rate more than rescue therapy (OR, .65; CI, .50 to .84) but the incidence of CLDN in the groups of survivors had not changed significantly (OR, .85; CI, .69 to 1.06). Only some of the natural surfactants of human,⁴ bovine,^{5–7} or porcine^{8–10} origin were used in these comparative stud-

ies and not the synthetic surfactants ALEC and EXOSURF and the natural bovine surfactants Survanta and Alv(e)ofact. The two trials,^{4,5} that included relatively small groups of infants did not show any benefit for using surfactant prophylactically instead of therapeutically. A meta-analysis of the surfactants that included more than 600 infants in their studies and without any correction or adjustment showed similar outcomes for the two Infasurf (=CLSE)^{6,7} and three Curosurf trials.^{8–10} The odds for mortality reduced significantly after prophylaxis (Infasurf: OR, .50; CI, .31 to .80; and Curosurf: OR, .52; CI, .36 to .76) and were lower for CLDN, but not statistically significant (Infasurf: OR, .76; CI, .56 to 1.03; and Curosurf: OR, .70; CI, .47 to 1.03). However, the impression that the incidence of CLDN has declined could change into rejection or acceptance of such an effect when ORs are adjusted for confounders.

Curosurf has, as other surfactants, proven its clinical efficacy by reducing the mortality rate and the incidence of severe RDS in rescue and multiple dose trials^{15–17} and also in prophylaxis versus rescue trials.^{8–10} In this study, individual data instead of general effect measures were available and the effect of adjustment of ORs for covariates within a meta-analysis for this surfactant could be shown. The important intertrial differences may be considered to be the weakness of this study. Rescue treatment was started at different stages of RDS in the three trials. The Dutch-Swedish trial had a 6 hours postpartum plus fraction of inspired oxygen ≥ 6 entry-criterion and only neonates suffering from severe RDS were given surfactant. For the Italian and French trials the entry criteria for rescue treatment (a mildly or moderately reduced respiratory condition of the neonate, and independent of postnatal age) were similar to those of the other prophylaxis versus rescue studies.^{4–7} The entry criteria for rescue treatment of the latter two trials are close to the criteria that neonatologists currently use. One might expect that because of the late treatment in the Dutch-Swedish trial, this trial has resulted in the largest differences in outcomes between the prophylactic and rescue treatment arms. Then the mean ORs for the three trials (as shown above) may differ more from one than without the Dutch-Swedish results. However, the opposite was true: after exclusion of the Dutch-Swedish results the difference from one became larger. We have kept the Dutch-Swedish results within this meta-analysis be-

TABLE 4. Outcomes per Country and Odds Ratio for Severe RDS, Mortality, and CLDN

	The Netherlands			Italy			France			Sweden			COMBINED RESULTS Mantel-Haenszel			Adjusted OR
	Prophylaxis Treatment	Rescue Treatment	Odds ratio	Prophylaxis Treatment	Rescue Treatment	Odds ratio	Prophylaxis Treatment	Rescue Treatment	Odds ratio	Prophylaxis Treatment	Rescue Treatment	Odds ratio	Prophylaxis Treatment	Rescue Treatment	Odds ratio	
Severe RDS*	+	14	47	18	24	0.65	8	11	0.55†	64	96	0.50	64	96		
	-	35	85	110	95	0.64	25	22		275	227	[0.33-0.74]	275	227		
Odds ratio		0.36	0.53	0.65			0.64						0.55†		0.50 [0.33-0.74]	
Neonatal Mortality	+	4	46	15	23	0.54	5	4		52	83	0.47	52	83		
	-	38	86	119	99		28	29		293	243	[0.30-0.73]	293	243		
Odds ratio		0.31	0.48	0.54			1.29						0.52		0.47 [0.30-0.73]	
CLDN 28-day-survivors	+	20	17	38	43		2	6		72	77	0.54	72	77		
	-	18	69	81	56		26	23		221	166	[0.34-0.86]	221	166		
Odds ratio		1.82	0.51	0.61			0.29						0.67		0.54 [0.34-0.86]	

* RDS data on nine French neonates were not available, because of death shortly after delivery (n = 4) or because these data were not recorded. † The Mantel-Haenszel odds ratios were corrected for the random effects term within country. The adjusted odds ratios take into account the random effects term and the effect of the significant covariates gender, birth weight, and prenatally given corticosteroids.

cause the meta-analysis is then as inclusive as possible and gives real estimates of the effect which one might anticipate for this surfactant.

Adjusting the ORs of the Curosurf studies for the significant differences that were present for the probability of mortality, severe RDS, and CLDN between the countries did not change these ratios substantially. Furthermore, the effect on the outcomes could not be attributed to the length of time after birth before rescue treatment was started (that is for most of the infants when RDS was still mild or moderate), or to the number of doses used for prophylaxis or for rescue treatment. This means that, independent of all differences, the actual treatment effect does not differ between the countries. A test to detect heterogeneity of ORs after stratification by country, was nonsignificant for each of the outcomes. Although the power to discriminate true differences is weak for tests of homogeneity, the result of this analysis suggests that the assumption of a common OR (treatment effect) over all trials is warranted. The results do not, however, show what is the best protocol for (multiple) prophylactic or rescue treatment.

All data stem from randomized trials and, after merging the four databases, there is strictly speaking, no need to incorporate the covariates in the model except to increase the power of the analysis or to correct for imbalances. There should not exist any confounding because treatments were randomly allocated. That this was indeed the case, was verified for all analyses by comparing the unadjusted OR (measuring the treatment effect on the outcome) with the adjusted one after incorporating gestational age, BW, gender, antenatal administration of corticosteroids, multiple pregnancy, and the method of delivery in the random-effects logistic model. After adjustment the power of the analysis increased but the differences between the adjusted and unadjusted ORs were not significant. Adjustment of the CLDN OR for confounders as BW, gestational age, gender, and corticosteroids demonstrates that the incidence of CLDN was significantly lower after prophylactic administration than after rescue treatment. The number of infants with CLDN has not decreased, but its incidence has. This is the result of larger number of survivors after prophylaxis and most likely also of less severe RDS after this type of intervention. In many randomized surfactant trials the ORs for the outcome, death plus BPD, is given. We believe that it is wrong to group the infants who died with those who will often survive without serious problems. (eg, the OR = 1 for the outcomes 7% mortality plus 3% CLDN in group A and 3% mortality plus 7% CLDN in group B). Therefore we have intentionally excluded this finding, although the odds for death plus BPD were lower after prophylaxis than after rescue treatment.

Independent of surfactant therapy, the prenatal administration of glucocorticosteroids resulted in the well-known effect of lowering the odds for mortality and RDS. There was no effect on the incidence of CLDN, probably because of the relatively low percentage of prenatally treated newborns (19%). The odds for CLDN on day 28 of neonates without RDS

are significantly lower than for those suffering from severe RDS (RRR, 46%; OR, .36; CI, .22 to .59). It is therefore better to prevent than to cure RDS because the absence of RDS will result in reduced risks for developing CLDN,¹⁸ even at 36 weeks' postconceptional age.¹⁹

The prophylactic administration of surfactant is a significant factor ($P < .01$) in reducing the odds for mortality and severe RDS, and therefore also for CLDN. BW, gestational age, gender, and the prenatal administration of glucocorticosteroids are important confounders. Thus, prophylaxis should be considered as the best therapeutic approach for those newborns, who have increased risks for developing RDS and CLDN. We hypothesize that similar effects can also be obtained with natural surfactants other than Curosurf.

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Mortality, Severe Respiratory Distress Syndrome, and Chronic Lung Disease of the Newborn Are Reduced More After Prophylactic Than After Therapeutic Administration of the Surfactant Curosurf

Johannes Egberts, Roland Brand, Hervé Walti, Giulio Bevilacqua, Gérard Bréart MD
and Fabrizio Gardini

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