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Randomized European Multicenter Trial of Surfactant Replacement Therapy for Severe Neonatal Respiratory Distress Syndrome: Single Versus Multiple Doses of Curosurf

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ABSTRACT. There is now convincing evidence that the severity of neonatal respiratory distress syndrome can be reduced by surfactant replacement therapy; however, the optimal therapeutic regimen has not been defined. This randomized European multicenter trial was designed to determine whether the beneficial effects of a single large dose of Curosurf (200 mg/kg) in babies with severe respiratory distress syndrome (arterial to alveolar oxygen tension ratio ~0.10) could be enhanced by using multiple doses of surfactant. Preterm neonates (birth weight 700 to 2000 g) with severe respiratory distress syndrome requiring artificial ventilation with fraction of inspired oxygen ≥0.6 were randomized into two groups at an age of 2 to 15 hours. Both groups received the usual dose of Curosurf (200 mg/kg) immediately after randomization. In neonates randomized to receive multiple-dose treatment, two additional doses of Curosurf (100 mg/kg each) were instilled into the airways (12 and 24 hours after the initial dose) provided that the patients still needed artificial ventilation with fraction of inspired oxygen >0.21. In both groups (single dose: n = 176, multiple doses: n = 167) there was a rapid improvement in oxygenation as reflected by a threefold increase in arterial to alveolar oxygen tension ratio within 5 minutes after surfactant instillation ($P < .001$), and peak inspiratory pressure and mean airway pressure could be reduced significantly during the first 6 hours after surfactant treatment. In addition, ventilatory requirement (peak inspiratory pressure, ventilatory efficiency index) was reduced in the multiple-dose group 2 to 4 days after randomization ($P < .05$ to $.01$). Sixty-five percent of the patients randomized to the multiple-dose regimen and 68% of the single-dose group needed supplemental oxygen 12 hours after the first treatment. Analysis of 28-day outcome data showed a reduction of the incidence of pneumothorax in the multiple-dose group (9% vs 18%, $P < .01$). The primary end point, of combined incidence of mortality and bronchopulmonary dysplasia, was 33% in the single-dose group and 27% in the multiple-dose group ($P = .08$). Mortality at 28 days was reduced from 21% in the single-dose group to 13% in the multiple-dose group ($P < .05$ by logistic regression). It is concluded that treatment with multiple doses of surfactant is more effective than single-dose treatment in severe neonatal respiratory distress syndrome, further reducing pneumothorax and mortality. *Pediatrics* 1992;89:13–20; *respiratory distress syndrome, pulmonary surfactants, neonates.*

ABBREVIATIONS. RDS, respiratory distress syndrome; a/A Po_2, arterial to alveolar oxygen tension ratio; BPD, bronchopulmonary dysplasia; Fio_2, fraction of inspired oxygen; PIP, peak inspiratory pressure.

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There is now convincing evidence that the severity of neonatal respiratory distress syndrome (RDS) can be reduced by either prophylactic treatment with surfactant[1–7] or surfactant replacement in neonates with established disease.[8–20] The surfactants used in these trials were derived from animal lungs[1,2,4,8,9,11–16,18,19] or human amniotic fluid[3,10,17] or were synthetic.[6,7] The short-term therapeutic response to exogenous natural surfactant includes a rapid improvement in oxygenation as reflected by increased arterial to alveolar oxygen tension ratio (a/APo_2) and reduced ventilatory requirements.[10,12–15,21] Well-designed randomized trials of surfactant treatment for established RDS have demonstrated reduced mortality,[1,3,13,15,18] lowered incidence of pulmonary interstitial emphysema[1,3,10,13,15,18] and pneumothorax[1,3,10,12,15,16,18,21]

and—more importantly—increased survival without chronic lung disease.[3,10,13,15,18] Despite these improvements, bronchopulmonary dysplasia (BPD) remains an important problem in survivors.

Data from a recent randomized trial on the effects of bovine surfactant in babies of more than 30 weeks' gestation with moderately severe RDS ($a/aPO_2 \sim 0.30$) suggest that a single dose of 100 mg/kg is insufficient in many cases and that babies who relapse may benefit from multiple doses.[21] The effect of the multiple-dose regimen on outcome variables could not be analyzed in this study because of the small sample size. The present trial was designed to determine whether the beneficial effects of a single large dose of Curosurf (200 mg/kg) in babies with very severe RDS ($a/aPO_2 \sim 0.10$) could be enhanced by using additional smaller doses in babies with a suboptimal response or those showing relapse.

METHODS

Characterization of Surfactant

Curosurf is a preparation of polar lipids, isolated from minced pig lungs by a combination of washing, centrifugation, extraction with chloroform-methanol, and liquid-gel chromatography.[22] It contains approximately 99% lipids, mainly phospholipids, and 1% low-molecular-weight, hydrophobic apoproteins (SP-B and SP-C).[22] In a pulsating bubble system at 37°C, Curosurf (diluted to 10 mg/mL) has a minimum surface tension of 0 mN/m within 10 minutes of area oscillation.[22] Tracheal instillation of Curosurf (160 mg/kg) leads to a striking improvement of lung function both in immature newborn rabbits[9] and in surfactant-depleted adult animals.[23] Further details of our quality-control protocol are described elsewhere.[22]

Study Design

The primary end point of the study was the combined incidence of mortality and BPD. On the basis of the results of the European Multicenter Trial,[15] we aimed at a reduction from 45% in the single-dose group to 25% in the multiple-dose group. Assuming a power of 90% and a significance level of 5% (two-tailed) we estimated that at least 150 babies in each group had to be randomized.

Fifteen European neonatal intensive care units collaborated in this trial. The number of patients randomized by each unit varied because of differences in the size of the population from which they were recruited, admission policies, and the duration of trial participation (Table 1).

TABLE 1. Number of Patients Randomized in Each Contributing Unit

Contributing Units	No. of Patients		
	Single Dose	Multiple Doses	Total
Amsterdam	7	10	17
Belfast	12	11	23
Bochum	17	17	34
Bonn	2	2	4
Braunschweig	10	6	16
Bremen	7	4	11
Essen	25	27	52
Göttingen	21	20	41
Graz	8	6	14
Groningen	4	2	6
Hannover	15	16	31
Koln	36	33	69
Mannheim	10	12	22
Paris	6	5	11
Stockholm	4	2	6
Total	184	173	357

The criteria for entry were the same as those of our previous controlled trial[15] and included (1) birth weight 700 to 2000 g, (2) age at treatment 2 to 15 hours, (3) clinical and radiological findings typical of neonatal RDS, (4) requirement of artificial ventilation with a fraction of inspired oxygen (FIO_2) ≥ 0.6, and (5) no complicating disease.

Neonates were not enrolled if there was evidence of prolonged rupture of membranes (≥3 weeks), intraventricular hemorrhage of grade III or IV, birth asphyxia (Apgar score ≤3 at 5 minutes, umbilical arterial cord pH <7 1; early onset of seizures), or major congenital anomalies (eg, chromosomal aberrations, Potter's syndrome, severe cardiovascular malformations, myelomeningocele). Anemia, hypotension, hypoglycemia, acidosis, and pneumothorax were treated by appropriate measures before surfactant replacement.

At randomization, all neonates were mechanically ventilated with an $FIO_2 \geq 0.60$ (entry criterion), a frequency of 40 to 60 breaths per minute, a peak inspiratory pressure (PIP) of <40 cm H_2O, a positive end-expiratory pressure of 3 to 5 cm H_2O, and an inspiration to expiration ratio of 1:1 to 1:2.

The babies were randomized to single-dose or multiple-dose regimen by means of sealed opaque envelopes, stratified for birth weight (700 to 1200 g and 1201 to 2000 g) and for center. Immediately after randomization all patients received 200 mg of Curosurf per kilogram (2.5 mL/kg) divided in two portions instilled into each main bronchus as previously described.[15] Patients in the multiple-dose group received two additional doses of Curosurf (100 mg/kg per dose) 12 hours and 24 hours after the first treatment if they still needed supplemental oxygen ($FIO_2 > 0.21$) and mechanical ventilation. The dose of 100 mg/kg for the additional doses was chosen for two reasons: first, the indication for retreatment ($FIO_2 > 0.21$) implied that these neonates would be less ill than at study entry; second, we did not want to cause overloading of the surfactant clearance pathways. Following each surfactant instillation, the neonates were ventilated manually for 1 minute using the same FIO_2 as before the replacement maneuver. The patients were then reconnected to the respirator, and the FIO_2 and respirator settings were immediately adjusted to the patients' clinical response to maintain adequate blood gas values (PaO_2 50 to 70 mm Hg, 6.6 to 9.2 kPa; $PaCO_2$ 40 to 45 mm Hg, 5.3 to 5.9 kPa; pH > 7.3) with the lowest possible levels of FIO_2 and PIP. The study was not conducted in a blind manner because that would have required a separate dosing team for each contributing center.

No suctioning of the airways was performed during the first 6 hours after surfactant instillation. Arterial blood gas values were determined at regular intervals (5, 15, 30, and 60 minutes; 2, 4, 6, 12, and 24 hours, 2, 3, 4, 5, 6, 7, and 10 days after surfactant replacement). The single- and multiple-dose groups were compared with respect to the following measurements: FIO_2, PaO_2, $PaCO_2$, pH, PaO_2/FIO_2 ratio, a/aPO_2, PIP, mean airway pressure, and arterial blood pressure. In addition, the groups were compared for the frequency of pulmonary and extrapulmonary complications as well as duration of mechanical ventilation and total time receiving supplemental oxygen.

Chest roentgenograms were obtained before treatment and at 12 hours and 28 days after randomization and whenever clinically indicated. Ultrasonographic examination of the head was performed serially and intracerebral hemorrhage was classified according to Papile et al.[24] Sequential echocardiograms were obtained every 24 hours to diagnose patency of the ductus arteriosus. Bronchopulmonary dysplasia was defined as requirement of more than 21% oxygen at 28 days of life plus typical findings in chest roentgenograms as judged by a pediatric radiologist.

The trial was approved by the ethics committee of each collaborating unit. Informed consent was obtained from the parents of the babies prior to randomization. The study protocol allowed for two interim analyses by the safety-monitoring committee, one after enrollment of one third of the patients and the second after enrollment of two thirds. In addition to detecting possible adverse effects, the safety-monitoring committee used stopping rules including a significance level of .001 for a difference in the primary end point between the treatment groups.[25]

Statistical Analysis

Baseline differences between the groups with respect to gestational age, birth weight, sex, age, and FIO_2 at randomization were evaluated by the Wilcoxon test and the χ^2 test, respectively. Logistic

TABLE 2. Number of Patients Excluded From the Analysis and Causes of Exclusion

Exclusion Criteria	No. of Patients	
	Single Dose	Multiple Doses
Severe congenital anomalies (hypoplastic left heart syndrome, bilateral chylothorax, tracheoesophageal malformation)	...	3
Birth weight		
<700 g	1	...
>2000 g	1	1
F_{IO_2}* < 0.6	...	2
Age at randomization > 15 h	5	...
Asphyxia (Apgar score ≤ 3 at 5 min)	1	...

* Fraction of inspired oxygen.

regression analysis was used to assess the effect of multiple-dose surfactant treatment on various dependent variables (pulmonary interstitial emphysema, pneumothorax, intracerebral hemorrhage, patent ductus arteriosus, BPD, mortality, and the combined incidence of death and BPD). The incidence of each of these complications was simultaneously controlled for the influence of the following independent variables: birth weight, sex, and allocation to different hospitals. Odds ratios representing approximate relative risks, corrected for the influence of the other independent variables, and 95% confidence intervals were calculated for each outcome parameter. The limit level of statistical significance was defined as 5%.

RESULTS

Characteristics of Patients

A total of 184 patients were randomized to the single-dose group and 173 to the multiple-dose group. Fourteen babies were retrospectively excluded from the final analysis because the entry criteria had been violated (underlying diseases, birth weight, age, and F_{IO_2} at randomization) (Table 2). Their exclusion took place blindly with respect to the outcome variables. Neither the baseline characteristics of the trial population (Table 3) nor the outcome results (see below) changed because of the exclusion of these patients.

Gas Exchange and Ventilator Setting After Surfactant Replacement

Treatment with Curosurf (200 mg/kg) resulted in a rapid improvement in oxygenation. As a consequence, the median F_{IO_2} could be lowered within 15 minutes from 0.85 to 0.35 in the single-dose and from 0.90 to 0.40 in the multiple-dose group (Fig 1A). Between 24 hours and 3 days neonates treated with multiple doses needed less oxygen compared with patients in the single-dose group ($P < .001$ at 24 and 48 hours; $P < .05$ at day 3).

The reduction of the F_{IO_2} corresponded to a threefold improvement of both the Pa_{O_2}/F_{IO_2} ratio (Fig 1B) and a/A P_{O_2} (Fig 1C). The Pa_{O_2}/F_{IO_2} ratio and a/A P_{O_2} at 24 and 48 hours were increased in the multiple-dose group compared with the single-dose group ($P < .01$ at 24 hours; $P < .05$ at 48 hours). Within 6 hours, PIP could gradually be reduced from 23 to 18 cm H_2O in both the single-dose and the multiple-dose group (Fig 2A) with a concomitant reduction in mean airway pressure from 13.0 to 9.0 and from 13.0 to 9.8, respectively (Fig 2B). From 2 to 4 days after randomization, PIP (Fig 2A) was lower in patients treated with multiple doses compared with the single-dose group and mean airway pressure and frequency were also reduced in the multiple-dose group compared with the single-dose group (Fig 2, B and C). The ventilatory efficiency index[26] was increased in the multiple-dose group 2 to 4 days after randomization (Fig 2D). Values for inspiration-expiration ratio, positive end-expiratory pressures, arterial blood pressure, Pa_{CO_2}, and pH showed no differences between the groups (data not shown).

Of the 167 patients in the multiple-dose group, 58 (35%) required one dose; 42 (25%) required two doses, and 67 (40%) needed three doses. Overall, 109 babies (65%) required additional doses. In the single-dose group, 120 (68%) of 176 patients would have qualified for additional doses.

Short-term Outcome (0 to 28 Days)

The outcome data are summarized in Table 4. Values for duration of artificial ventilation and total time of exposure to supplemental oxygen showed no difference between the groups. The combined incidence of mortality and BPD was 33% in babies randomized to single-dose treatment and 27% in the multiple-dose group, representing a 20% relative reduction of the primary end point. Mortality at 28 days, one component of the primary end point, was reduced from 21% in the single-dose group to 13% in the multiple-dose group (for statistical evaluation, see below). During the first 7 days mortality was 18% in the single-dose group and 11% in the multiple-dose group. In the single-dose group death from respiratory failure was 46% (17/37), and in the multiple-

TABLE 3. Characteristics of Patients

Characteristics	No. of Patients (n = 357)*		No of Patients (n = 343)	
	Single Dose (n = 184)	Multiple Doses (n = 173)	Single Dose (n = 176)	Multiple Doses (n = 167)
Gestational age, wk (mean ± SD)	29.2 ± 2.5	28.9 ± 2 2	29.2 ± 2.5	28.9 ± 2.2
Birth weight, g (mean ± SD)	1222 ± 345	1193 ± 331	1218 ± 327	1189 ± 321
Male, no. (%)	103 (56.0)	96 (55.5)	99 (56.3)	91 (54.5)
Age at randomization, h†	6.1 (4 6–11.0)	6.7 (4.4–9.7)	6.0 (4.5–10.5)	6.7 (4.4–9.7)
F_{IO_2}‡ at randomization†	0.85 (0.7–1.0)	0 90 0.71–1 0)	0.83 (0.7–1.0)	0.90 (0.72–1.0)

* Total number of patients randomized to single- or multiple-dose treatment prior to exclusion of 14 patients for violation of entry criteria as specified in Table 2.
† Median (25th–75th percentile).
‡ Fraction of inspired oxygen.

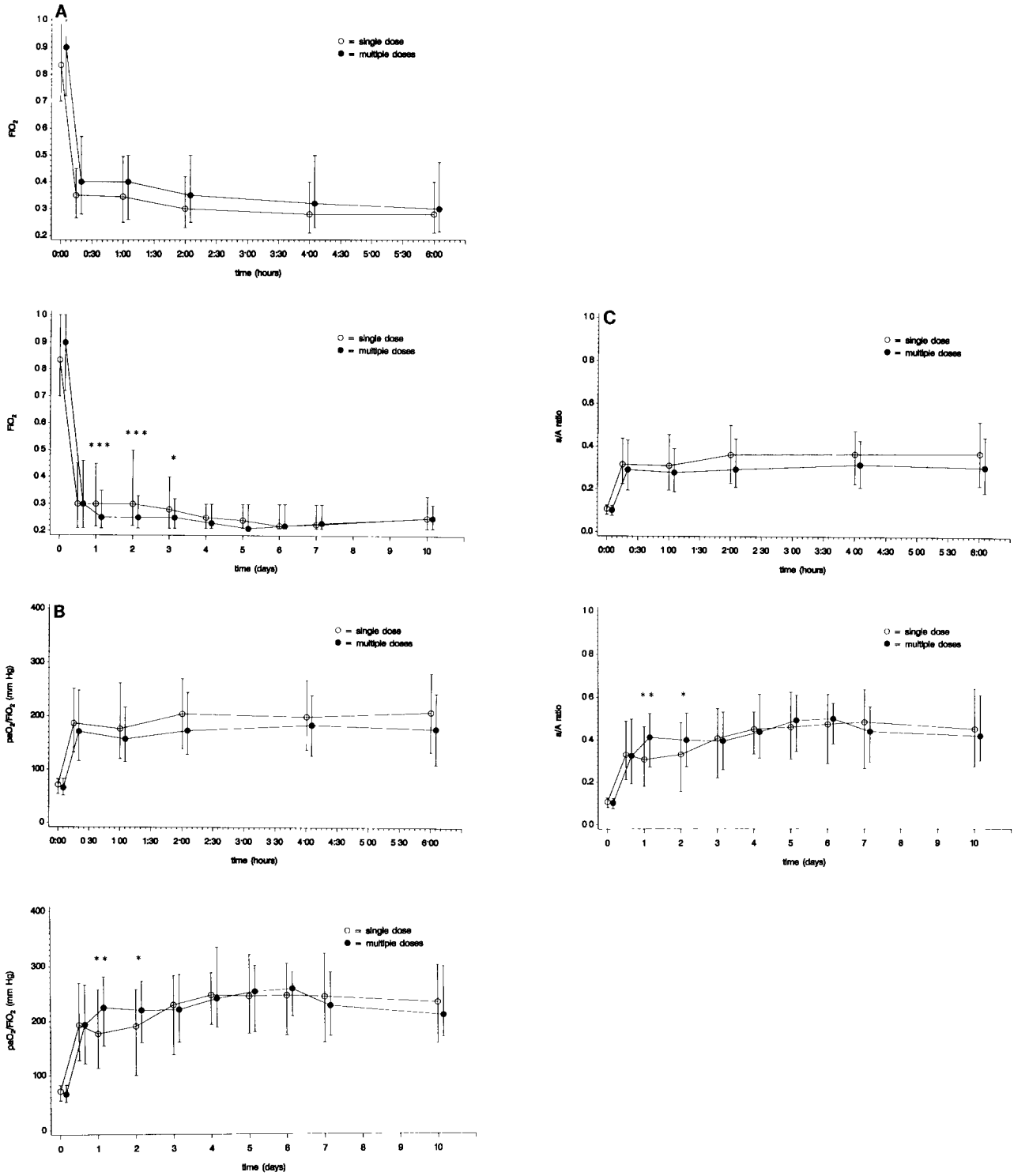

Fig. 1. Oxygenation measurements in neonates treated with a single dose or multiple doses of Curosurf at various intervals after randomization. The points for the two groups are offset for clarity. Values are given as median and 25th to 75th percentile. Conversion factor: 7.52 mm Hg = 1 kPa. *$P < .05$, **$P < .01$, ***$P < .001$. FIO_2, fraction of inspired oxygen.

dose group it was 41% (9/22). Overall, 85% of the babies who died of respiratory failure had pneumothorax.

The incidence of pneumothorax was reduced from 18% in patients treated with a single dose to 9% in those who received multiple doses of surfactant ($P < .01$). For pulmonary interstitial emphysema, intracerebral hemorrhage (all grades), patent ductus arteriosus, BPD, septicemia, and necrotizing enterocolitis, there were no significant differences between the groups.

The differences in outcome parameters between the groups were present also prior to exclusion of patients for violation of entry criteria. Among the total of 184 patients randomized to single-dose treatment, the mortality at 28 days was 21%, and among 173 babies randomized to multiple doses it was 13% ($P < .05$). The corresponding incidence figures for

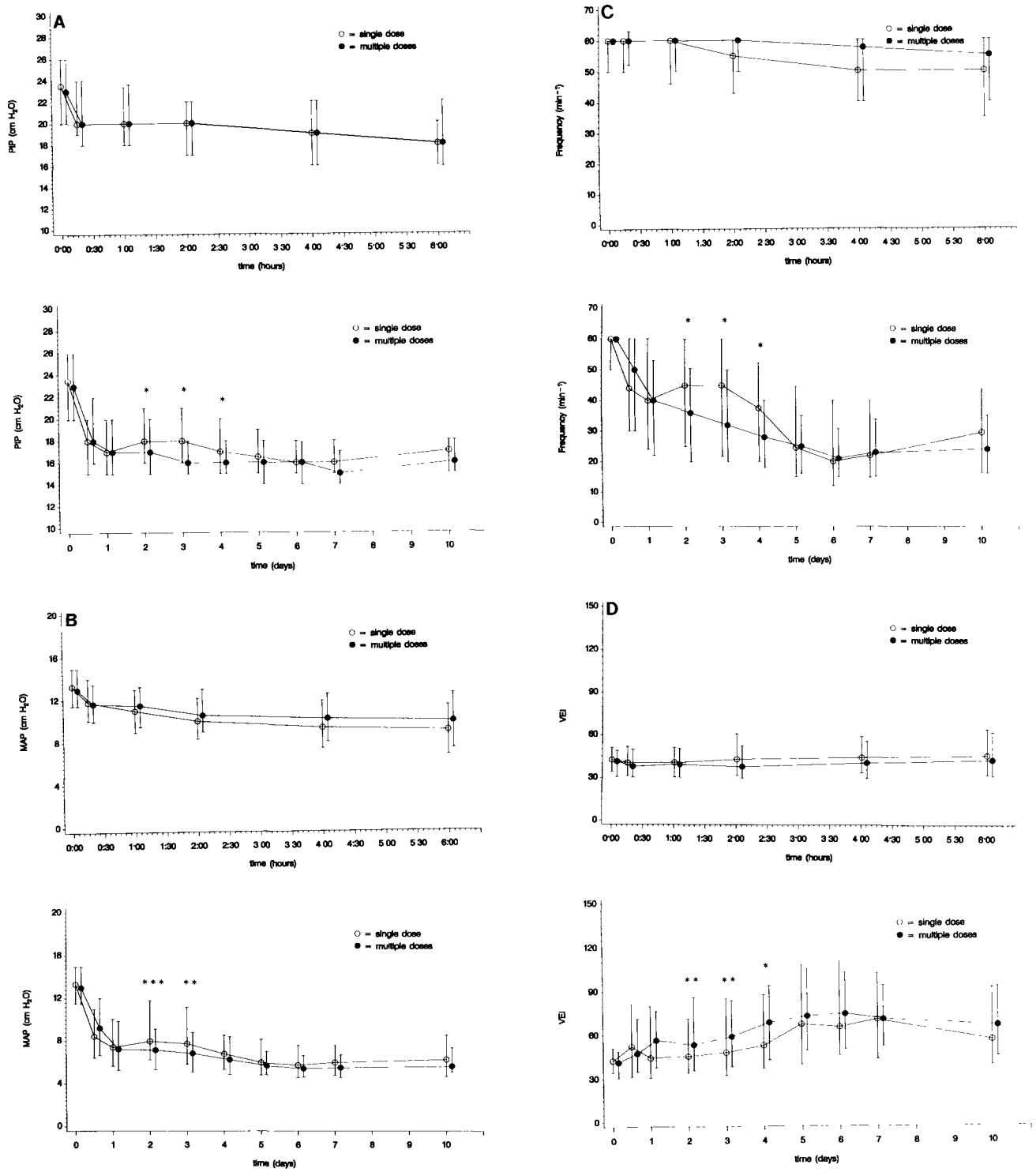

Fig. 2. Peak inspiratory pressure (PIP, A) mean airway pressure (MAP, B), ventilatory frequency (C), and ventilatory efficiency index (VEI, D) in patients treated with a single dose or multiple doses of Curosurf at various time intervals after randomization. Values are given as median and 25th to 75th percentile. The points for the two groups are offset for clarity. Conversion factor: 10 cm H_2O = 1 kPa. VEI = $\frac{3800}{(\text{frequency} \times P \times P_{CO_2})}$; P = PIP-positive end-expiratory pressure measured in millimeters of mercury.
* $P < .05$, ** $P < .01$, *** $P < .001$.

pneumothorax were 18%, and 9%, respectively ($P < .05$).

Odds ratios for various outcome parameters and 95% confidence intervals calculated from the logistic regression model are shown in Table 5. The odds ratios for pneumothorax and neonatal death among patients randomized to multiple-dose treatment were significantly reduced. Low birth weight was a very strong risk factor for intracerebral hemorrhage, BPD, and death. The influence of gender on the outcome variables did not reach statistical significance (except for the combined incidence of mortality and BPD),

TABLE 4. Outcome for Patients at 28 Days of Age

Outcome Parameters	Single Dose (n = 176)	Multiple Doses (n = 167)
Duration of artificial ventilation in survivors, h*	322 (62–>672)	360 (26–>672)
Total time of exposure to oxygen in survivors, h*	446 (24–>672)	420 (26–>672)
Complications, no. (%)		
Pulmonary interstitial emphysema	48 (27)	38 (23)
Pneumothorax	32 (18)	15 (9)
Pulmonary hemorrhage	4 (2)	3 (2)
Intracerebral hemorrhage		
Total	75 (43)	71 (43)
Grade I–II	41 (23)	33 (20)
Grade III–IV	34 (20)	38 (23)
PDA†	91 (52)	93 (57)
BPD‡	21 (12)	22 (13)
Septicemia	35 (20)	22 (13)
Necrotizing enterocolitis	5 (3)	5 (3)
Mortality	37 (21)	22 (13)
Mortality/BPD‡	58 (33)	44 (27)

* Median (25th–75th percentile).
† Patent ductus arteriosus.
‡ Bronchopulmonary dysplasia.

TABLE 5. Logistic Regression Analysis: Odds Ratios and 95% Confidence Intervals*

Outcome Parameters	Randomization (Multiple Doses vs Single Dose)	Birth Weight (1201–2000 vs 700–1200 g)	Sex (Female vs Male)
Pulmonary interstitial emphysema	0.77 (0.46–1.28)	0.66 (0.30–1.12)	0.99 (0.58–1.68)
Pneumothorax	0.39 (0.19–0.80)‡	0.70 (0.35–1.40)	0.56 (0.27–1.15)
Intracerebral hemorrhage	1.01 (0.63–1.63)	0.33 (0.20–0.55)§	0.74 (0.45–1.21)
PDA	1.23 (0.79–1.93)	0.68 (0.43–1.09)	1.20 (0.75–1.91)
BPD	1.12 (0.57–2.23)	0.36 (0.17–0.76)‡	0 64 (0.31–1.33)
Mortality	0.50 (0.25–0.99)†	0.05 (0.02–0.16)§	0.60 (0.29–1.24)
Mortality/BPD	0.60 (0.34–1.07)	0.08 (0.04–0.17)§	0.49 (0.27–0.90)†

* Symbols denote the P value for testing the hypothesis that the odds ratio equals 1. PDA, patent ductus arteriosus; BPD, bronchopulmonary dysplasia.
† $P < .05$.
‡ $P < .01$.
§ $P < .001$.

but nearly all odds ratios indicated a higher risk for male babies.

DISCUSSION

Respiratory distress caused by surfactant deficiency[27] remains the most common cause of death and handicap in preterm neonates. Improved survival occurred with the introduction of mechanical ventilation, although this type of treatment may lead to significant complications such as pulmonary air leaks and BPD.

The introduction of surfactants from natural sources to treat established RDS was a major breakthrough in neonatal medicine.[8] Surfactants derived from animal lungs or human amniotic fluid are composed mainly of phospholipids, although the precise formula of each differs depending on the manufacturing procedure. Human surfactant isolated from amniotic fluid by sucrose-gradient centrifugation contains the large hydrophilic apoprotein (SP-A) and has a total protein content of approximately 5%.[3] "Rescue" trials with this type of surfactant have used a lower dose of phospholipids (60 mg/kg) but have permitted subsequent dosing[3,10]; in other trials reduction in mortality and complications have been achieved with a single dose of surfactant.[12–19] Our present data indicate that in babies with severe RDS the beneficial effects of a single large dose of Curosurf (200 mg/kg) can be further improved by a multiple-dose regimen.

Irrespective of whether the baby was allocated to single- or multiple-dose treatment, administration of the initial dose of surfactant substitution resulted in rapid improvement of gas exchange as reflected by a significant increase in Pao_2/Fio_2 and $a/A\ Po_2$ ratios, and Fio_2 could be rapidly reduced in both groups of babies. However, between 24 hours and 3 days after surfactant replacement, neonates treated with multiple doses needed less oxygen than patients in the single-dose group. In both groups the PIP and mean airway pressure could be reduced significantly during the first 6 hours after surfactant instillation; such a striking effect of the initial surfactant dose has been reported only by Fujiwara and coworkers.[14,18] From 2 to 4 days after randomization, patients in the multiple-dose group had a lower pressure and frequency and a higher ventilatory efficiency index than babies

allocated to single-dose treatment. This difference in ventilatory requirement might explain the lower incidence of pneumothorax and mortality in the multiple-dose group. However, the total time of artificial ventilation and exposure to supplemental oxygen was similar in both groups of patients.

In the first European multicenter trial of surfactant replacement,[15] mortality rate was 51% in control subjects and 31% in Curosurf-treated neonates, reflecting the severity of RDS. In the present trial, which had the same entry criteria, mortality was even lower (21%) among patients randomized to single-dose treatment. This fact may represent improving skills of the hospital staff responsible for the management of these very sick patients during the phase of rapidly changing lung function and circulatory readjustment that usually follows surfactant replacement. Following multiple doses of Curosurf, mortality was further reduced (13%) and the same holds for the incidence of pneumothorax (9% vs 18%). These effects of multiple doses were confirmed by logistic regression analysis. The incidence of BPD was similar in both groups, but compared with our previous trial there was a trend toward a further increased number of surfactant-treated babies surviving without evidence of chronic lung disease (55% in the first European trial vs 67% of patients randomized to single-dose treatment in the present study, and 73% of patients randomized to multiple doses).

For the primary end point of the study, the combined incidence of mortality and BPD, the multiple-dose treatment resulted in a 20% relative reduction but this impact of surfactant replacement was not statistically significant. This negative result is probably related to an incorrect assumption in our original sample size calculation. On the basis of the first European multicenter trial,[15] we estimated that 45% of patients in the single-dose group would die or develop BPD before the age of 28 days, but in the present study only 33% did so. Therefore, our sample size was too small to establish a statistical significance for a reduction in this end point with sufficient power. Nevertheless, our data provide strong evidence that the incidence of air leak complications and neonatal death in babies with severe RDS can be further reduced by using multiple doses of Curosurf.

The average pattern of a sustained therapeutic response, obtained in the present study with a large initial dose of surfactant (200 mg/kg), is clearly different from the average pattern of relapse noted in less sick babies treated with a lower dose of bovine surfactant extract (100 mg/kg).[21] These combined observations lend additional support to our original concept that babies with RDS benefit from receiving a high dose of surfactant and furthermore indicate that subsequent doses should be given if the baby remains dependent on supplemental oxygen, without awaiting a severe relapse.

An important challenge for future trials is to lower the incidences of BPD and intracerebral hemorrhage. The overall incidence of intracerebral hemorrhage after instillation of Curosurf was similar in both groups of this trial (43%) and only slightly reduced (not significant) when compared with data from the first Curosurf trial (47% in surfactant-treated patients).

We conclude that treatment with multiple doses of surfactant is more effective than single-dose treatment in severe neonatal RDS, further reducing ventilatory requirement, pneumothorax, and mortality. The multiple-dose regimen may also increase the pool size of alveolar surfactant lipids available for recycling during the recovery phase of the disease.

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COMPASSIONATE PEDIATRICS

Dear Matthew,

Oh, Matthew, I love you so much. It's so hard to see you go. I wish your life could have been more than hospitals and needle sticks and tests and sickness. I had such great hopes for you. Looking at your big hands, my hands, I imagined watching you build great things with them. And your smiles. When you smiled at me I felt more joy than I have ever felt in my life. You have a fighting spirit so strong that I can only hope that mine will match it when I need it.

I never expected to see you go before me. I knew it was possible, but I just didn't think it would happen. I imagined us going camping and walking in the woods with the dogs. I imagined playing in the yard and tinkering with cars and bikes.

It's hard to see you go but I want you in no more pain. I want you to experience joy and happiness—peacefulness, which you really have yet to discover. A part of me is going with you. You remind me so much of myself and your mother. When I look into those beautiful blue eyes that are so familiar I wonder what you are thinking. I wish you could realize how much joy and inspiration you have given me, and I hope that somehow we have given you some joy and comfort in return.

It's so hard to see you go,
I'll miss you,

DAD

SUBMITTED BY ROBERT H. WHARTON, MD