# Nasal Continuous Positive Airway Pressure and Early Surfactant Therapy for Respiratory Distress Syndrome in Newborns of Less Than 30 Weeks' Gestation

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**ABSTRACT.** *Objective.* **To determine whether early versus late treatment with porcine surfactant (Curosurf) reduces the requirement of mechanical ventilation in very preterm infants primarily supported by nasal continuous positive airway pressure (nasal CPAP).**

*Design.* **Multicenter randomized, controlled trial.**

*Patients.* **The study population comprised 60 infants <30 weeks' gestation with respiratory distress syndrome (RDS) who had an arterial to alveolar oxygen tension ratio (a/APO$_2$) of 0.35 to 0.22.**

**The cohort from which the study population was generated comprised 397 infants.**

*Results.* **The need for mechanical ventilation or death within 7 days of age was reduced from 63% in the late-treated infants to 21% in early-treated infants. Increasing numbers of antenatal steroid doses also improved the outcome, especially in the early-treated infants. Six hours after randomization mean a/APO$_2$ rose to 0.48 in the early-treated infants compared with 0.36 in the late-treated. The need of mechanical ventilation before discharge was reduced from 68% in the late-treated to 25% in the early-treated infants.**

*Conclusions.* **Nasal CPAP in combination with early treatment with Curosurf significantly improves oxygenation and reduces the subsequent need for mechanical ventilation in infants <30 weeks' gestational age with RDS.** *Pediatrics* 1999;103(2). URL: http://www.pediatrics.org/cgi/content/full/103/2/e24; *respiratory distress syndrome, pulmonary surfactant, Curosurf, nasal continuous positive airway pressure.*

ABBREVIATIONS. RDS, respiratory distress syndrome; nasal CPAP, nasal continuous positive airway pressure; a/APO$_2$, arterial to alveolar oxygen tension ratio; Fio$_2$, fraction of inspired oxygen; TcPo$_2$, transcutaneous partial pressure of oxygen; TcPco$_2$, transcutaneous partial pressure of carbon dioxide; PDA, patent ductus arteriosus; NEC, necrotizing enterocolitis; BPD, bronchopulmonary dysplasia; IVH, intraventricular hemorrhage; PVL, periventricular leucomalacia; ROP, retinopathy of prematurity.

In a randomized, controlled study we have shown that a single dose of surfactant (Curosurf, Chiesi Farmateutici, Parma, Italy) given by short-lasting intubation reduces the need for mechanical ventilation and improves oxygenation in infants with moderate to severe respiratory distress syndrome (RDS) treated with early nasal continuous positive airway pressure (nasal CPAP).[1] Very few pulmonary and extrapulmonary complications were observed in these infants. However, some of the surfactant-treated infants supported by nasal CPAP developed apnea despite good oxygenation and needed mechanical ventilation for that reason. In the same trial, there seemed to be a higher need for ventilation among infants randomized relatively late after birth and in infants with relatively low birth weight. From the literature we know that surfactant given prophylactically,[2–4] or as early treatment to infants requiring mechanical ventilation,[5] is more effective than late rescue treatment.

The present study was designed to test the hypothesis that infants <30 weeks' gestation with RDS, requiring no other ventilatory support than supplemental oxygen and nasal CPAP, would do better when treated with surfactant at an early stage of the disease compared with treatment at a moderately advanced stage, which according to traditional criteria, would indicate treatment with surfactant. In particular, we were eager to find out whether early intervention could reduce more effectively the need for mechanical ventilation during the subsequent clinical course.

We also described the cohort of infants <30 weeks' gestation from which the study population was generated, with particular reference to the incidence of RDS, disease severity, and current treatment routines. A main principle for treatment of these infants was initiation of nasal CPAP at the first signs of respiratory distress after birth.

## METHODS

The trial was conducted at 11 Danish neonatal centers from April 1, 1995 through January 22, 1997.

### Randomization, End Points, Study Definitions, and Ethical Aspects

*Patients and Randomization*

Infants 2 to 72 hours of age with a gestational age <30 weeks, treated for RDS with nasal CPAP ≥6 cm of water were random-

ized if the arterial to alveolar oxygen tension ratio $(a/APo_2)$[6] was 0.35 to 0.22 and decreased over a period of >30 minutes. These values correspond to a fraction of inspired oxygen $(Fio_2)$ of 0.37 to 0.55 when $Po_2$ is 75 mm Hg and $Pco_2$ is 50 mm Hg. The diagnosis of RDS was based on at least two of the four classic symptoms: need of supplemental oxygen, tachypnea, intercostal retractions and grunting, and exclusion of other causes of respiratory failure.[7] The severity of RDS was graded radiologically,[8] but chest radiography was not obligatory before randomization because we wanted to avoid unnecessary delay of treatment with surfactant. Exclusion criteria were Apgar score ≤2 at 5 minutes, prolonged rupture of the membranes >3 weeks, lethal malformations, pneumonia, and incompletely treated pneumothorax. In twins only the first twin to fulfill the criteria was randomized. The infants were randomly assigned to receive a single dose of Curosurf either immediately after randomization (early treatment) or when $a/APo_2$ had decreased further to a level of 0.21 to 0.15 $(Fio_2$ 0.57–0.77), remaining <0.22 for >30 minutes (late treatment). The randomization was central. Sets of numbered opaque envelopes, one for each participating center, were opened sequentially on request by telephone from the attending neonatologist. Blocks of four were used to ensure that an equal number of infants were enrolled in each treatment group in each center.

The lightweight system based on Benveniste's pediatric gas-jet valve (Dameca, Copenhagen, Denmark)[9–11] was used for nasal CPAP by all the participating units. Prophylaxis with theophylline or caffeine was optional.

Continual monitoring of the transcutaneous partial pressures of oxygen $(TcPo_2)$ and carbon dioxide $(TcPco_2)$ (Marquette-Hellige, Milwaukee, WI; or Radiometer, Copenhagen, Denmark) was obligatory from the establishment of nasal CPAP. $TcPo_2$ values around 75 mm Hg were what we aimed for, and $a/APo_2$ was calculated from the transcutaneous values with intervals no longer than 30 minutes from the age of 2 hours until randomization. The arterial partial pressure of oxygen and carbon dioxide are closely correlated to the corresponding transcutaneous values in hemodynamically stable infants.[12,13]

Curosurf at a dose of 200 mg (2.5 mL) per kg body weight was given in two bolus fractions of 100 mg/kg each, instilled via the tracheal tube with a few minutes interval. Manual ventilation was given for 2 to 5 minutes after each dose. As soon as respiratory movements and $TcPo_2$ were satisfactory, the infant was extubated (usually within 10 minutes). Morphine (0.1 mg/kg intravenously) before intubation, and Naloxone (0.01 mg/kg intravenously) before extubation were optional. The clinical efficacy of Curosurf in infants supported by mechanical ventilation is well-documented.[14–16]

### Primary End Point

The primary end point was the need for mechanical ventilation or death within 7 days of birth. The indications for mechanical ventilation were $a/APo_2$ values <0.15 decreasing further over a period of >30 minutes, severe apnea defined as >4 episodes per hour or need of mask ventilation >2 times per hour, or inability of extubation within 1 hour after intubation for surfactant treatment. Pressure-limited, time-cycled, continuous flow ventilation was used initially.

### Secondary End Points

The secondary end point was $a/APo_2$ 6 hours after randomization, need for mechanical ventilation before discharge, mortality before discharge, and incidence of pneumothorax, pulmonary hemorrhage, patent ductus arteriosus (PDA), and necrotizing enterocolitis (NEC). PDA was diagnosed by clinical signs, ultrasonography, or both, NEC was diagnosed on clinically grounds only. In survivors we also calculated the incidence of bronchopulmonary dysplasia (BPD), intraventricular hemorrhage (IVH), periventricular leucomalacia (PVL), retinopathy of prematurity (ROP), duration of oxygen treatment, duration of nasal CPAP, and duration of mechanical ventilation. BPD was defined as prolonged oxygen requirement and was recorded at day 28 as well as at a postconceptional age of 36 weeks. IVH was diagnosed 5 to 7 days after birth and classified according to Papile et al.[17] PVL was diagnosed by ultrasonography[18] 4 to 6 weeks after birth. ROP was evaluated at a postnatal age of 10 weeks.

Informed written parental consent was required either prenatally or early postnatally with the purpose of randomizing quickly

when needed. Because of the nature of the intervention, blinding was not attempted. The research ethics committee at each center approved the trial.

## Sample Size Calculation and Statistical Analysis

On the basis of data from infants <30 weeks' gestation in our previous randomized study,[1] we estimated a reduction in the need of mechanical ventilation or death from 65% in the late treated infants to 40% in the early treated. Assuming a power of 90% and a significance level of 5% (two-tailed), we estimated that 178 infants had to be randomized. So as not to lose statistical power by unbalanced confounders, we decided to include 200 patients, and estimated the study time to 18 months.

Data were collected by the local clinical coordinators on data sheets. These were sent for input centrally and were not revealed until final analysis.

When the trial had run for 22 months with the inclusion of only 60 patients, an interim analysis was performed. The stopping criterion was a $P$ value <.05 for the primary end point, or if the $P$ value was >.05 along with a judgment by the consulting statistician and an independent observer that a significant result could not be obtained within 24 months.

In the two treatment groups the characteristics of the infants at the time of randomization and the secondary outcome parameters were compared using either Mann-Whitney test or $\chi^2$ test (depending on whether the variable was continuous or categorical). A logistic regression analysis was used to investigate possible associations between the success rate (defined as the proportion of infants who survived for >7 days without needing mechanical ventilation) and the following variables: gestational age, birth weight, age at randomization, sex, antenatal steroid treatment, and type of surfactant treatment (early or late). The influence of these variables on $a/APo_2$ after 6 hours was evaluated using an ordinary multiple regression analysis. The intent-to-treat was the main principle of the statistical evaluation. The analyses were repeated for infants fulfilling the entry criteria strictly, but these data are only shown when different from the main analysis. $P$ values <.05 were considered to indicate statistical significance.

## The Cohort of Infants <30 Weeks' Gestation

The cohort of infants <30 weeks' gestation born in the participating centers in the trial period were grouped with regard to severity of RDS; and mode of respiratory support, surfactant therapy, and mortality before discharge were described for each of these groups.

The definitions used for severity of RDS were mild RDS when $a/APo_2$ remained above 0.35 during the first 72 hours of life; severe RDS when mechanical ventilation was needed within 24 hours (main indications: $a/A Po_2$ <0.15 or severe apnea); and moderate RDS in all other cases.

### RESULTS

The interim analysis performed after randomization of 60 patients showed that significantly fewer early-treated than late-treated infants needed mechanical ventilation or died within 7 days. The trial was therefore stopped. The result was unchanged (same $P$ value) after exclusion of 6 infants (2 from the early-treated and 4 from the late-treated group) not strictly fulfilling the entry criteria and 1 from the early-treated group who was not given surfactant.

## Characteristics of Patients

The characteristics of the patients in the two treatment groups showed no significant differences at randomization (Table 1). The mean values of $a/APo_2$ and $TcPco_2$ (Table 1) indicate a population with moderate severity of RDS at randomization. Ninety-three percent of the infants had radiographic RDS. This was severe in 14, moderate in 27, and mild in 15 infants. Four infants had normal chest films. In 3 of these the first chest film was taken after surfactant

**TABLE 1.** Characteristics of Patients at Randomization

| Characteristic | Early-treated Group (n = 33) | Late-treated Group (n = 27) | P |
|---|---|---|---|
| | Median (Range) | | |
| Birth weight (g) | 950 (665–1600) | 935 (618–1555) | .84 |
| Gestational age (wk) | 27 (25–29) | 28 (25–29) | .54 |
| Age at randomization (h) | 4.1 (0.3–40.1)* | 4.5 (1.7–41.3)* | .55 |
| a/APo$_2$ at randomization | 0.28 (0.22–0.38)* | 0.28 (0.08–0.77)* | .69 |
| TcPco$_2$ (mm Hg) at randomization | 50 (34–103) | 47 (30–74) | .69 |
| | Number (%) | | |
| Male sex | 17 (52) | 18 (67) | .24 |
| Born in treating hospital | 30 (91) | 24 (89) | .20 |
| Cesarean section | 25 (76) | 17 (63) | .28 |
| Theophylline | 21 (64) | 18 (67) | .81 |
| Antenatal steroid | 26 (79) | 22 (81) | .80 |
| Two doses | 20 (61) | 17 (63) | .85 |

* In both treatment groups the lowest age at entry was 2.0 hours and the range of a/APo$_2$ was 0.22 to 0.35 for infants fulfilling the entry criteria strictly (n = 54). One infant in each treatment group was randomized before 2 hours; the late-treated also had a/APo$_2$ <0.22. One infant treated early and 3 infants treated late had a/APo$_2$ >0.35.

treatment. In 1 case the chest film was normal at the age of 2 hours, 2 hours before surfactant treatment. No significant differences were found between the groups.

Nasal CPAP was begun 1 to 120 minutes after birth at a median age of 17 minutes, and the infants were randomized at a median age of 4.3 (0.3–41) hours. The early-treated infants received surfactant at a median age of 5.2 (1–45) hours; and the late-treated at a median age of 9.9 (3.8–43) hours (P = .07). Mean values for a/APo$_2$ at the time of surfactant treatment were 0.26 ± 0.06 in the early-treated infants and 0.16 ± 0.04 in the late-treated (P < .0001).

The symptoms leading to mechanical ventilation were a/APo$_2$ <0.15 in 59% and apnea in 41% of the cases without significant differences between the groups. Two late-treated infants and 2 early-treated could not be extubated after surfactant instillation (50% because of a/APo$_2$ <0.15 and 50% because of apnea) and were subsequently treated with mechanical ventilation. The median maximum peak inspiratory pressure required within 24 hours for ventilated infants was 23 (range 16–30) cm of water in both treatment groups. Only 3 infants in each group received an extra dose of surfactant in combination with mechanical ventilation. None needed 2 additional doses.

### Regression Analysis

The logistic regression analysis showed that the relation between type of treatment and success rate was highly significant (P = .0013; Table 2) and could not be explained by the influence of other variables included in the analysis. Furthermore, we found that increasing the number of antenatal steroid doses improved the success rate (P = .01), and this effect was most prominent in the early-treated group. More infants in the lower weight classes than those in the higher weight classes received two or more doses of antenatal steroid.

Except for the type of treatment (P = .02), none of the variables included in the analysis influenced a/APo$_2$ 6 hours after randomization (Table 2); however, there was a trend towards higher values in infants treated with two or more doses of antenatal steroid.

### Secondary Outcome Measures

The need for mechanical ventilation before discharge was reduced from 68% in the late-treated infants to 25% in the early-treated infants ( P = .005; Table 2).

Very few cerebral and extracerebral sequelae were found in either treatment group (Tables 3 and 4). Fewer early- than late-treated infants developed PDA (P < .02) and none of them needed surgical closure.

Nine infants randomized to late treatment did not receive surfactant because a/APo$_2$ remained >0.22. Three of them needed mechanical ventilation.

### The Cohort of Infants <30 Weeks' Gestation

The total number of infants <30 weeks' gestation admitted to the participating units in the study period was 397 corresponding to 0.4% of all 98 100 liveborns. The gestational age was 27.2 ± 1.6 wk and the birth weight was 1033 ± 274 g. A total of 80% received antenatal steroid and 42% surfactant. The

**TABLE 2.** Data on Study End Points

| End point | Early Treatment | Late Treatment | P Value | Statistics |
|---|---|---|---|---|
| Mechanical ventilation and/or death <7 days, number (%) | 7 (21) | 17 (63) | .0013 | Logistic regression |
| Mechanical ventilation and/or death before discharge, number (%) | 9 (27) | 19 (70) | .004 | $\chi^2$ |
| Mechanical ventilation before discharge, number (%) | 8 (25) | 17 (68) | .005 | $\chi^2$ |
| a/APo$_2$ after 6 hours, mean ± SD | 0.48 ± 0.18 | 0.36 ± 0.18 | .02 | Multiple regression |

**TABLE 3.** Secondary Outcome Parameters Before Discharge (Total Study Population)

| | Curosurf | | P |
|---|---|---|---|
| | Early Treatment (n = 33) | Late Treatment (n = 27) | |
| Mortality | 3 (9)* | 7 (26) | .16 |
| Pneumothorax | 0 | 1 (4) | .92 |
| Pulmonary hemorrhage | 0 | 0 | 1.00 |
| Patent ductus arteriosus | 10 (30) | 16 (59) | .02 |
| Needing surgery | 0 | 0 | 1.00 |
| Necrotizing enterocolitis | 5 (15) | 5 (19) | 1.00 |
| Needing surgery | 1 (3) | 1 (4) | .56 |

\* The figures represent numbers and (percent).

**TABLE 4.** Secondary Outcome Parameters Before Discharge (Survivors)

| | Curosurf | | P |
|---|---|---|---|
| | Early Treatment (n = 30) | Late Treatment (n = 20) | |
| | Number (%) | | |
| Bronchopulmonary dysplasia | | | |
| Oxygen day 28 | 11 (37) | 8 (40) | .81 |
| Oxygen postconceptional week 36 | 1 (3) | 1 (4) | .66 |
| Intraventricular hemorrhage | | | |
| Grades 1–2 | 5 (15) | 2 (7) | .80 |
| Grades 3–4 | 1 (3) | 0 | .84 |
| Periventricular leucomalacia | 0 | 0 | 1.00 |
| Retinopathy of prematurity | 3 (9) | 2 (7) | .63 |
| Cryotheraphy | 1 (3) | 1 (4) | .66 |
| | Median (Range) | | |
| Oxygen treatment (day) | 6.5 (0.3–69) | 18.5 (0.5–64) | .54 |
| Nasal CPAP (day) | 38.5 (0.8–64) | 39.0 (12–155) | .76 |
| Mechanical ventilation* (day) | 2.5 (1.2–5.5) | 2.1 (0.3–13.9) | .47 |

\* Six early-treated and 12 late-treated surviving infants were ventilated.

overall mortality was 18%. A total of 94% of the infants were initially treated with nasal CPAP, and 30% needed mechanical ventilation within 7 days.

A total of 54% had no or mild RDS when supported by nasal CPAP. This group had very little need of surfactant (1%) and a low mortality (3%). A total of 26% had moderate to severe RDS and were either randomized in the trial (15%) or had a corresponding disease severity (11%). These latter infants could not be randomized because of protocol restrictions or because the attending neonatologist was tied up by emergency work on other patients. Infants with severe RDS were treated with surfactant in 90% and 48% died.

## DISCUSSION

Our strategy for clinical management of neonatal RDS includes three main sequential steps besides the prophylactic use of antenatal steroids: early nasal CPAP, surfactant administered to infants while they are still breathing spontaneously, and mechanical ventilation in cases of progressive respiratory failure, if necessary in combination with repeated treatment with surfactant.

In the first hours after birth nasal CPAP has ad-

vantages over oxygen supplementation and is a good alternative to mechanical ventilation.[19–23] The mission of this form of early ventilatory support is to keep the lungs open, thereby avoiding potentially harmful iterated collapse and reexpansion of terminal airspaces.[24,25] By a similar mechanism, CPAP may prevent excessive consumption of surfactant in newborn infants with limited supply of this material in the air-spaces.[26] CPAP also has a well-documented preventive effect on apnea.

The recruitment of infants for the present study was slower than expected. Apparently, when planning the trial, we underestimated the power of nasal CPAP to prevent the development, or progression, of RDS in these immature infants. Considerably more infants could have been randomized if the second twin and infants with a postnatal age <2 hours had been eligible for randomization. On the other hand, the effect of early surfactant treatment on the primary end point was much greater than expected in our sample size calculations, and a highly significant result was obtained after randomization of only 60 patients. Among infants who received two doses of antenatal steroid the outcome in the early-treated group was even better, but in the late-treated group the steroid effect was no longer evident. Infants treated with two doses of steroid had a lower mean birth weight than those who received none or a single dose of steroid, probably because there were more cases of emergency delivery among the largest infants. The difference between $a/APo_2$ at the time of surfactant treatment in the early- versus late-treated infants was highly significant. In contrast, the difference in median age from birth to surfactant treatment between the groups did not quite reach statistical significance. These results indicate that the progression of RDS symptoms accelerates when $a/APo_2$ decreases below 0.36. Because 54% of the cohort of infants <30 weeks' gestation had no need for surfactant and in the light of the results of the controlled trial, surfactant treatment as soon as $a/APo_2$ decreases below 0.36 seems appropriate.

Infants randomized to late rather than early treatment had a higher incidence of PDA that could probably be attributed to disease severity. The exact effect of surfactant on cardiopulmonary hemodynamics is not well-understood, but it seems that shunting through the ductus is present in all infants with RDS and that it is neither initiated nor increased by surfactant therapy.[27]

In a former controlled trial[1] evaluating the effect of Curosurf in infants on nasal CPAP with RDS and $a/APo_2$ <0.22, 43% of the infants randomized to surfactant therapy required mechanical ventilation and 62% of the subgroup with gestational age <30 weeks needed this treatment. This is close to the corresponding figure for infants randomized to late treatment in the present trial, 63%. In the same controlled trial[1] significantly fewer boys than girls needed mechanical ventilation after surfactant treatment. We have had a secondary look at the former treatment group and found that more boys than girls accidentally had a gestational age above 29 weeks (64% vs 43%) and probably for that reason the boys

had a better response. In the present study the success rate for avoiding mechanical ventilation was equal for boys and girls in both treatment groups. Therefore, we believe that nasal CPAP combined with surfactant is an effective treatment in both sexes.

Although we prefer nasal CPAP as the initial treatment for RDS, we also maintain that in infants needing mechanical ventilation this additional support should, if possible, be provided before serious deterioration of the clinical condition has occurred. On the basis of previous experience,[1] a/APo$_2$ <0.15 was chosen as indication for mechanical ventilation. With this strategy there were very few pulmonary and extrapulmonary sequelae in both treatment groups despite the fact that 68% of the patients had moderate to severe RDS. The initial period of spontaneous breathing made possible by nasal CPAP and the relatively early administration of surfactant probably contribute to this favorable outcome in both treatment groups. For infants requiring mechanical ventilation, the total median time of 2.5 days of ventilator treatment in the present study was shorter than in other trials of rescue surfactant therapy for moderate to severe RDS.[16,28] Furthermore, a single dose of surfactant (200 mg/kg) was enough to reverse the clinical course in most of our present patients whereas in other rescue studies two or more doses of natural[15,28,29] or synthetic surfactant[30] were often required for a sustained response. The total dose of natural surfactant used in these studies was in most cases higher than in the present trial.

The effectiveness of our treatment strategy is also reflected by the overall mortality of 18% for the cohort of 397 infants with gestational age <30 weeks. Nearly all of them received early nasal CPAP. For comparison, the mortality for infants with gestational age <30 weeks was 30% in a Danish total population of infants with RDS treated with nasal CPAP without surfactant,[20] and 16% in a Swedish total population of somewhat more mature infants with a birth weight <1500 g, who in 51% of the cases were treated with early nasal CPAP.[31] The mortality of mechanically ventilated infants <30 weeks' gestation given rescue treatment with natural modified surfactant ranged from 17% to 25%.[3,4,28] The mortality was 12% to 15% in prophylactically treated infants.[3,4]

## CONCLUSION

In summary, about half of the cohort of newborns with a gestational age <30 weeks can be treated effectively with nasal CPAP alone, and at least 25% with early nasal CPAP and surfactant. Early treatment with surfactant, administered during a short period of intubation to infants with a/APo$_2$ decreasing to <0.36, is a cost-effective intervention (moderate use of surfactant, very few complications) that significantly reduces the subsequent need for mechanical ventilation.

## ACKNOWLEDGMENTS

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