Very Early Surfactant Without Mandatory Ventilation in Premature Infants Treated With Early Continuous Positive Airway Pressure: A Randomized, Controlled Trial

Article *in* PEDIATRICS · February 2009

DOI: 10.1542/peds.2007-3501 · Source: PubMed

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Pediatrics 2009;123;137-142
DOI: 10.1542/peds.2007-3501

SPECIAL ARTICLE

Very Early Surfactant Without Mandatory Ventilation in Premature Infants Treated With Early Continuous Positive Airway Pressure: A Randomized, Controlled Trial

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The authors have indicated they have no financial relationships relevant to this article to disclose.

ABSTRACT

BACKGROUND. Chronic lung disease is one of the most frequent and serious complications of premature birth. Because mechanical ventilation is a major risk factor for chronic lung disease, the early application of nasal continuous positive airway pressure has been used as a strategy for avoiding mechanical ventilation in premature infants. Surfactant therapy improves the short-term respiratory status of premature infants, but its use is traditionally limited to infants being mechanically ventilated. Administration of very early surfactant during a brief period of intubation to infants treated with nasal continuous positive airway pressure may improve their outcome and further decrease the need for mechanical ventilation.

OBJECTIVE. Our goal was to determine if very early surfactant therapy without mandatory ventilation improves outcome and decreases the need for mechanical ventilation when used in very premature infants treated with nasal continuous positive airway pressure soon after birth.

DESIGN/METHODS. Eight centers in Colombia participated in this randomized, controlled trial. Infants born between 27 and 31$^{6/7}$ weeks' gestation with evidence of respiratory distress and treated with supplemental oxygen in the delivery room were randomly assigned within the first hour of life to intubation, very early surfactant, extubation, and nasal continuous positive airway pressure (treatment group) or nasal continuous airway pressure alone (control group). The primary outcome was the need for subsequent mechanical ventilation using predefined criteria.

RESULTS. From January 1, 2004, to December 31, 2006, 279 infants were randomly assigned, 141 to the treatment group and 138 to the control group. The need for mechanical ventilation was lower in the treatment group (26%) compared with the control group (39%). Air-leak syndrome occurred less frequently in the treatment group (2%) compared with the control group (9%). The percentage of patients receiving surfactant after the first hour of life was also significantly less in the treatment group (12%) compared with the control group (26%). The incidence of chronic lung disease (oxygen treatment at 36 weeks' postmenstrual age) was 49% in the treatment group compared with 59% in the control group. All other outcomes, including mortality, intraventricular hemorrhage, and periventricular leukomalacia were similar between the groups.

CONCLUSIONS. In premature infants treated with nasal continuous positive airway pressure early after birth, the addition of very early surfactant therapy without mandatory ventilation decreased the need for subsequent mechanical ventilation, decreased the incidence of air-leak syndrome, and seemed to be safe. Reduction in the need for mechanical ventilation is an important outcome when medical resources are limited and may result in less chronic lung disease in both developed and developing countries. *Pediatrics* 2009;123:137–142

www.pediatrics.org/cgi/doi/10.1542/peds.2007-3501

doi:10.1542/peds.2007-3501

This trial has been registered at www.clinicaltrials.gov (identifier NCT00563641).

Key Words
very early surfactant, early nasal continuous positive airway pressure, respiratory distress syndrome, preterm infant, mandatory ventilation

Abbreviations
CLD—chronic lung disease
MV—mechanical ventilation
RDS—respiratory distress syndrome
NCPAP—nasal continuous positive airway pressure
Fio_2—fraction of inspired oxygen
Spo_2—pulse oximetry saturation
PPV—positive-pressure ventilation
PIE—pulmonary interstitial emphysema
IVH—intraventricular hemorrhage
PVL—periventricular leukomalacia
RR—relative risk
CI—confidence interval

Accepted for publication Mar 27, 2008

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IMPROVEMENTS IN THE care of premature infants in recent decades have enabled the survival of more immature infants, with an increase in morbidities such as chronic lung disease (CLD).[1] Contrary to expectations, newer modes of mechanical ventilation (MV), and other medical therapies, have not reduced the incidence of CLD.[2] In fact, MV has been implicated as a strong risk factor for CLD.[3–7] Studies performed in animals have demonstrated that barotrauma and volutrauma during MV contribute to lung damage[8–10] and that lung damage occurs after only a few breaths of MV with ventilator settings similar to those used for premature infants with respiratory distress syndrome (RDS).[11] These observations suggest that developing interventions that decrease the need for MV may prevent CLD. One strategy is to use nasal continuous positive airway pressure (NCPAP) as an alternative to MV in spontaneously breathing infants. Epidemiologic studies have repeatedly demonstrated a lower incidence of CLD in centers at which NCPAP is used as the first line of therapy for premature infants with RDS.[4,5,12]

Prophylactic surfactant therapy improves the short-term respiratory status of premature infants, but its use is traditionally limited to infants intubated immediately after birth and placed on MV.[13] The addition of very early surfactant therapy to early NCPAP, during a brief period of intubation, may decrease the need for subsequent MV. This hypothesis is supported by the studies of Verder et al[14,15] and Reininger et al,[16] who demonstrated a reduction in the need for MV in infants with established RDS of moderate severity treated in this manner. In their studies, surfactant was used as a rescue therapy during a wide range of times after birth (up to 72 hours). Their results suggest the potential benefits of this treatment. However, conclusions about the safety of these interventions based on their data are limited by the small size of the studies. Also, these studies did not address the question of whether the use of very early surfactant therapy (within the first hour of life) in premature infants with clinical evidence of respiratory distress may further improve their outcome. This is a critical question because of the potential for this intervention to reduce morbidity associated with NCPAP and reduce the need for MV in a larger population of infants. Therefore, the purpose of this randomized, controlled trial was to determine if the addition of very early surfactant therapy to the early use of NCPAP in premature infants with respiratory distress who breath spontaneously after birth is superior to NCPAP alone in its ability to reduce the need for MV.

MATERIALS AND METHODS

From January 1, 2004, to December 31, 2006, we conducted a multicenter randomized, controlled trial in 8 tertiary NICUs in 3 cities in Colombia, South America (Bogotá, Bucaramanga, and Cali). Participating centers were categorized as either IIIA or IIIB special care nurseries.[17] Inclusion criteria were a gestational age of 27 to 31⁶⁄₇ weeks, postnatal age between 15 and 60 minutes, and supplemental oxygen requirement with evidence of increased work of breathing (tachypnea, intercostal retractions, nasal flaring, or grunting). Exclusion criteria were an Apgar score of <2 at 5 minutes, intubation during the first 15 minutes of life, prenatal diagnosis of major congenital anomalies, and prolonged rupture of membranes of >3 weeks' duration. Because of the system of payment for medical care in Colombia, some infants were transferred from their hospital of birth to centers approved by their payers when prolonged hospitalization was anticipated. Infants who were likely to be transferred to another center soon after birth were not enrolled in the study. Before delivery, parental consent was obtained for potential study participants. A computerized balanced block randomization scheme was used to generate group assignment of individual infants. Participants were stratified according to center and gestational age group (27–29 and 30–31⁶⁄₇ weeks' gestation). These assignments were contained in opaque, consecutive-numbered, sealed envelopes at each center that were opened by research personnel after eligibility was determined.

At birth, all infants were resuscitated in a standardized manner beginning with 100% oxygen as recommended in the *Textbook of Neonatal Resuscitation*.[18] The fraction of inspired oxygen (F_{IO_2}) was adjusted thereafter to maintain a pulse oximetry saturation (Spo_2) between 90% and 92% in Bucaramanga and Cali, and between 88% and 90% in Bogotá. For those infants requiring positive-pressure ventilation (PPV) with a face mask, a constant-flow PPV system (Neopuff infant resuscitator [Fisher & Paykel Healthcare, Inc, Auckland, New Zealand]) with a preset peak pressure of 20 cm H_2O and a positive-end expiratory pressure of 5 cm H_2O was used. Resuscitation areas were equipped with pulse oximeters and oxygen blenders.

Between 15 and 60 minutes of life, infants were continuously evaluated for the presence of increased work of breathing (as defined above) and the need for supplemental oxygen. Eligible infants were initially placed on NCPAP of 6 cm H_2O (Bubble CPAP system [Fisher & Paykel Healthcare, Inc]), and immediately a randomization envelop was opened to establish assignment either to early NCPAP plus very early surfactant (treatment group) or to early NCPAP alone (control group). Infants who were randomly assigned to the control group remained on NCPAP, whereas those assigned to the treatment group were temporarily intubated for surfactant administration. Before surfactant administration, correct position of the endotracheal tube was determined by length of the tube at the lip, symmetry of breath sounds, and chest wall rise. A modified natural bovine lung surfactant (Survanta [Abbott Laboratories, Abbott Park, IL]) was administered at a dose of 100 mg/kg in 2 aliquots, 2 minutes apart. PPV was administered by using the Neopuff infant resuscitator for 1 minute after each aliquot with the previously described pressures, followed by extubation to NCPAP with a pressure of 6 cm H_2O and a humidification temperature of 39°C. All participating infants received a loading dose of aminophylline (5 mg/kg intravenously), followed by a maintenance dose of 2.5 mg/kg every 12 hours, as long as they remained on NCPAP. Umbilical catheter place-

ment was left to the discretion of the attending physician.

All infants who met treatment-failure criteria (see below) were eligible to receive rescue surfactant therapy. Rescue doses of surfactant (doses after the initial dose in the treatment group and all doses in the control group) were administered under specified guidelines as follows. Infants in the control group who met treatment-failure criteria were intubated and placed on MV and subsequently received an initial dose of surfactant in a standardized manner as described for the treatment group. Gradual weaning of the ventilator settings then took place while maintaining Spo_2 within the preestablished ranges. If FIO_2 was weaned to <0.30, no additional doses of surfactant were administered; if FIO_2 was >0.30, additional doses were given every 6 hours until a total of 4 doses were administered. Surfactant was not administered beyond 72 hours of age. Infants in the treatment group who met treatment-failure criteria were intubated and placed on MV, and surfactant was administered in a standardized manner as previously described with a maximum of 4 doses, including the dose administered at the time of randomization.

To minimize variability among groups, all participating health care personnel were trained to resuscitate infants in a uniform manner by using the Neonatal Resuscitation Program,[18] and 2 workshops were conducted on the use of the Neopuff infant resuscitator and the Bubble NCPAP system before initiation of the study. A minimum of 2 pilot patients were required per center before initiation of the study. Outcome data for these infants are not included in the study results.

The primary outcome was the need for MV (treatment failure). Treatment failure was defined a priori by either failure of adequate oxygenation or ventilation as follows: (1) FIO_2 of >0.75 for >30 minutes to maintain Spo_2 within the preestablished target ranges; (2) persistent or recurrent desaturation below 80% that did not respond to suctioning of the airways and PPV; or (3) PCO_2 of >65 mm Hg and pH of <7.22 on an arterial or capillary blood gas analysis, in association with progressive respiratory failure. Infants in the treatment group who could not be extubated after their initial dose of surfactant because of clinical instability were analyzed as treatment failures. This study was not blinded; personnel providing care in the delivery room were sometimes responsible for subsequent care of study infants.

Secondary outcomes included neonatal mortality, pulmonary air leak (pneumothorax, pulmonary interstitial emphysema [PIE]), CLD (oxygen treatment at 36 weeks' postmenstrual age), subglottic stenosis, intraventricular hemorrhage (IVH),[19] periventricular leukomalacia (PVL),[20] rescue surfactant doses, duration of MV, duration of oxygen therapy, and length of hospitalization.

On the basis of historical data from study centers and data from a published trial that enrolled a similar population,[21] the incidence of MV among infants between 27 and 31 weeks' gestation who were not intubated immediately after birth was estimated to be 50%. We estimated that very early surfactant therapy would reduce the incidence of MV by 20%. A sample size of 134 infants per group was necessary to demonstrate this difference with an α value of .05 (2 tails) and a β value of .1. To allow for dropouts, a final sample of 279 infants was deemed appropriate. Comparisons between groups for dichotomous variables were conducted by using the Mantel-Haenszel test with adjustment for gestational age center strata. Continuous variables were compared with the t test from analysis of variance that adjusted for gestational age. Differences between gestational age strata were determined through exploratory posthoc analysis.

The study protocol was approved by the research ethics committees at all participating institutions. A safety review committee with 2 pediatricians trained in clinical epidemiology not involved in the study monitored mortality and morbidity after the enrollment of every 50 infants. The study would have been stopped if a significant excess of death in either group was observed at a $P \leq .05$ level at any given point of observation. All other morbidities were required to be at the $P \leq .001$ level. An interim analysis evaluating safety was planned when half the estimated sample population was enrolled.

RESULTS

During the study period, 805 infants with gestational ages of ≥ 27 and $\leq 31\frac{6}{7}$ weeks were born at the study centers. The parents of 43 infants refused consent; 8 were stillborn; and 96 either did not meet all eligibility criteria or had an exclusion. There were 379 infants who were potentially eligible but not enrolled: 257 were likely to be transferred to another institution soon after delivery, 58 were delivered emergently and study personnel were not available, and at the time of delivery of 64 infants, the Bubble NCPAP device was not available. The remaining 279 were enrolled in the study, 141 in the treatment group and 138 in the control group. One infant who was randomly assigned to the treatment group did not receive surfactant because of lack of availability at the time of delivery; this infant remained in the treatment group and was analyzed on an intent-to-treat basis. One infant who was randomly assigned to the control group was subsequently transferred and lost to follow-up before evaluating the primary outcome and was excluded from the final analysis. All remaining infants were followed until death or discharge to home. No significant differences were observed in mortality or morbidity during the interim analysis.

Baseline characteristics were similar between groups (Table 1). Table 2 lists the primary and major secondary outcomes. All infants in the treatment group were successfully extubated to NCPAP. Need for MV was significantly lower in the treatment group compared with the control group (26% vs 39%). There were no differences between groups in mortality rate. Pneumothorax and PIE were the only form of pulmonary air leak observed and were significantly less frequent in the treatment group compared with the control group (2% vs 9%). CLD was less frequent in the treatment group compared with the control group (49% vs 59%), although the

TABLE 1 **Baseline Characteristics in the Study Groups**

Characteristic	Control Group ($N = 137$)	Treatment Group ($N = 141$)
Birth weight, mean ± SD, g	1293 ± 324	1299 ± 325
Gestational age, mean ± SD, wk	29.3 ± 1.4	29.3 ± 1.4
Male, *n* (%)	67 (49)	78 (55)
5-min Apgar score, median (range)	9 (3–10)	8 (4–10)
C-section, *n* (%)	116 (84)	116 (82)
Prenatal steroids, *n* (%)	119 (88)	121 (88)
Chorioamnionitis, *n* (%)	7 (5)	10 (7)

Control group: early NCPAP only; treatment group: early NCPAP plus very early surfactant therapy.

TABLE 2 **Primary and Other Major Outcomes**

Outcome	Control Group ($N = 137$), *n* (%)	Treatment Group ($N = 141$), *n* (%)	RR (95% CI)
MV	53 (39)	37 (26)	0.69 (0.49–0.97)[a]
Mortality			
All deaths	13 (9)	13 (9)	1.00 (0.48–2.05)
<7 d	5 (4)	8 (6)	1.61 (0.54–4.75)
<28 d	12 (8)	11 (7)	0.91 (0.42–1.98)
≥28 d	1 (1)	2 (1)	2.06 (0.19–22.20)
Pneumothorax/PIE	12 (9)	3 (2)	0.25 (0.07–0.85)[a]
CLD[b]	73/124 (59)	63/128 (49)	0.84 (0.66–1.05)
IVH, grade III or IV	3 (2)	2 (1)	0.71 (0.12–4.16)
PVL	1 (1)	0	0.35 (0.01–8.64)

Control group: early NCPAP only; treatment group: early NCPAP plus very early surfactant therapy.

[a] $P \leq .05$.

[b] Oxygen treatment at 36 weeks' postmenstrual age; denominator = survivors to 36 weeks' postmenstrual age.

TABLE 3 **Secondary Outcomes**

Outcomes	Control Group ($N = 137$)	Treatment Group ($N = 141$)	*P*
Infants receiving rescue surfactant, *n* (%)	35 (26)	17 (12)	.0039
Days on NCPAP, mean ± SD	4.3 ± 3	4.6 ± 4.7	.561
Days on oxygen, mean ± SD	22.3 ± 17.4	20.9 ± 20.5	.524
Days on MV, median (IQR)	3.3 (8–12)	4.3 (4–67)	.169
Length of hospitalization, mean ± SD, d	36.9 ± 20.7	37.1 ± 21.3	.938

Control group: early NCPAP only; treatment group: early NCPAP plus very early surfactant therapy. IQR indicates interquartile range.

difference was not statistically significant. Other outcomes including incidence of grades 3 and 4 IVH and PVL were similar between groups. No complications of intubation were reported in either group. Treatment failure secondary to recurrent apnea was similar between groups: 10 (7.1%) of 141 in the treatment group versus 8 (5.8%) of 137 in the control group (relative risk [RR]: 1.21 [95% confidence interval (CI): 0.49–2.9]).

The need for rescue surfactant therapy was significantly lower for infants who were randomly assigned to the treatment group compared with those assigned to the control group (12% vs 26%; Table 3). No differences were observed between the groups in days on NCPAP, days on oxygen, days on MV, or length of hospitalization.

Posthoc comparisons between the treatment and control groups were performed in the 2 gestational age strata (27–29 and 30–31⁶⁄₇ weeks). A significant decrease in the need for MV in the treatment group was observed in the 30 to 31⁶⁄₇ weeks' gestation strata (9 of 69 [13.0%] vs 21 of 63 [33.3%]; RR: 0.39 [95% CI: 0.19–0.79]; $P = .006$) but not in the 27 to 29 weeks' gestation strata (28 of 72 [38.9%] vs 32 of 74 [43.2%]; RR: 0.90 [95% CI: 0.61–1.33]; $P = .59$). In a similar manner, the incidence of CLD was significantly lower in the treatment group in the 30 to 31⁶⁄₇ weeks' gestation strata (18 of 69 [26.1%]) vs 28 of 63 [44.4%]; RR: 0.59 [95% CI: 0.36–0.95]; $P = .027$) but not in the 27 to 29 weeks' gestation group (45 of 72 [62.5%] vs 45 of 74 [60.8%]; RR: 1.03 [95% CI: 0.80–1.33]; $P = .83$).

DISCUSSION

This study demonstrates that among premature infants with respiratory distress supported with NCPAP only, the addition of surfactant therapy immediately after birth during a brief period of intubation reduces the need for subsequent MV compared with the use of NCPAP alone. Specifically, this strategy reduces the need for MV from 39% among infants treated with NCPAP only to 26% among those who also received very early surfactant. Similar to the second study by Verder et al[15] (early versus late rescue surfactant), our study supports the observation that the earlier surfactant is administered to infants on NCPAP, the better the outcome. This strategy also seems to be safe, evidenced by the absence of complications of intubation and the similarity of complications associated with prematurity between study groups. The addition of very early surfactant therapy also reduces the likelihood of air-leak syndrome. This finding is not surprising, because a reduction in pulmonary air leaks has been observed as a benefit of surfactant therapy used in other ventilatory strategies for RDS.[13]

We believe that the improved outcomes observed among infants who were randomly assigned to the treatment group were attributable solely to the addition of very early surfactant with standardized PPV. A number of elements of the study design support this statement. All infants were resuscitated in a uniform manner by using a single type of ventilation system at identical inflation pressures. Enrollment occurred during the first hour of life, minimizing the confounding effects of exposures before study enrollment. The same NCPAP system was used for all infants, and all personnel were trained on its use before study initiation. Also, the same initial CPAP pressure was used for both the control and the treatment groups. Prophylactic use of aminophylline to minimize treatment failures secondary to apnea was standardized in both groups. Finally, and perhaps most importantly, strict criteria were developed for initiating MV, the primary end point of the study.

Our results are similar to those observed in previous studies of surfactant administration during a brief period of intubation in nonventilated infants.[14–16] However,

there were several important differences in study design between the current and previous studies. For example, compared with the studies of Verder et al,[14,15] infants in our study were treated with surfactant at a very early postnatal age (<60 minutes) and had less severe respiratory disease. Reininger et al[16] investigated a similar strategy in more mature infants compared with those in study population. In their study, NCPAP and surfactant therapy were initiated at a later postnatal age when clinical signs of moderate-to-severe respiratory distress were present, and varying methods of administrating NCPAP were used. Despite the differences in study design among these studies, all investigators have reported reductions in the need for MV in the range of 30% to 50%. Collectively, these studies suggest that surfactant therapy for infants on NCPAP reduces the likelihood of MV in a large population, including infants at a wide variety of gestational ages and severity of lung disease. Another important difference was the lower rate of treatment failure observed in our control group (39%) compared with that of other studies (Verder et al[14]: 85%; Verder et al[15]: 68%; Reininger et al[16]: 70%).[14–16] The lower rate of treatment failure in our control group may be explained by the standardization in the administration of PPV, limiting lung damage from the use of variable inflation pressures, and by the administration of prophylactic aminophylline with improved lung mechanics and reduced treatment failures secondary to recurrent apneas.[11,22] This observation is of particular interest to physicians working in health care settings where MV and surfactant therapy are not available and mortality resulting from respiratory failure is high.

Our study did not investigate the benefits of very early surfactant therapy to infants treated with NCPAP compared with the benefits after obligatory initiation of MV and prophylactic surfactant therapy. Comparison of these strategies was the subject of a previous small study by Dani et al[21] and is the subject of large, randomized trials yet to be published. The results of these studies will provide additional insight into the ideal strategy for early respiratory care of premature infants.

The primary end point of this study, the need for MV, was chosen because of its importance in the context of medical care systems in which resources are limited. For this reason, a reduction in the need for MV was felt to be valuable even if this benefit did not result in reductions of long-term adverse outcomes. This study was not powered to demonstrate a reduction in CLD, arguably a more important outcome where medical resources are not scarce. However, there was a 10% absolute reduction in CLD among infants who received early surfactant. This magnitude of benefit would be clinically relevant and is similar to that observed after other therapies for the prevention of CLD (eg, vitamin A).[23] It is possible that the observed differences in CLD between study groups resulted from either the study intervention or chance alone. When posthoc comparisons between the treatment and control groups were performed by using gestational age strata, the treatment group showed a significant decrease in the need for MV and a significantly lower incidence of CLD in the 30 to 31⁶⁄₇ weeks' gestational age group but not in the 27 to 29 weeks' gestational age group. A possible explanation for this observation may be a decrease in the effect of a single dose of surfactant as gestational age decreases.[24] Subsequent randomized trials powered to demonstrate a difference in CLD will be required to resolve this important issue.

Finally, a significant difference was observed in the need for rescue surfactant among infants in the treatment group compared with those in the control group. We speculate that the very early administration of surfactant facilitated lung recruitment and potentiated the maintenance of normal lung volumes compared with the use of NCPAP only. Improved lung volumes would minimize the need for increased ambient oxygen concentrations to maintain adequate blood oxygenation, reducing NCPAP failures and the provocation for subsequent surfactant therapy.

This study did not include infants born at very early gestational ages in whom the adverse effects of MV are common and serious. These infants were excluded for 2 reasons. First, in our study centers, at the earliest gestational ages (ie, 23–25 weeks), mortality rates are extremely high and intensive care is not universally provided. Second, at somewhat older gestational ages (ie, 25–26 weeks), on the basis of historical data, the need for MV during the early neonatal period was sufficiently high that it was deemed unethical to delay MV, and therefore prophylactic surfactant therapy, as would be required in the control group in this study. For these reasons, we cannot extrapolate the results of this study to infants with gestational ages of <27 weeks.

This study had some limitations. First, the study was not blinded, which could have resulted in biased decisions about initiating MV. We attempted to minimize the potential impact of this possibility by using strict criteria for initiating MV. In addition, investigators were required to report instances in which MV was initiated without these criteria having been satisfied; none were reported. Second, we did not use a definition for CLD that relied on a physiologic test for the need for supplemental oxygen. Although there was variability in the use of oxygen among centers resulting from different criteria for administration of oxygen and differences in altitude, we believe that the use of supplemental oxygen was consistent within each center. Therefore, the effect of variable use among centers in the evaluation of the study intervention was minimized by stratification according to center before randomization. The relatively high rates of CLD observed in both study groups, which seem to be higher than would be predicted in similar populations in the United States,[12] may be explained by differences in target oxygen saturation requirements and the use of oxygen at different altitudes (from sea level to 2600 m above sea level),[25] but this hypothesis requires additional investigation. Although we did not find complications from intubations in our study groups, it is possible that our sample size was not large enough to identify them. Future clinical trials should be powered to address this concern.

CONCLUSIONS

Among spontaneously breathing, premature infants treated with NCPAP immediately after birth, the addition of very early surfactant therapy without mandatory ventilation decreased the need for subsequent MV by ~33% and decreased the incidence of air-leak syndrome. This strategy also seems to be safe and cost-effective when used as a first line therapy for very premature infants with mild-to-moderate respiratory distress. The reduction in need for MV may be particularly advantageous in medical settings where resources are limited. These benefits may translate into a reduction in the incidence of CLD, suggested by the trend observed in this study.

ACKNOWLEDGMENTS

This research was supported by Vanderbilt University, Universidad Javeriana, University of North Carolina, Fisher & Paykel Healthcare, and Abbott Laboratories.

We thank the research coordinators, respiratory therapists, and bedside nurses involved in the care of study infants; without their valuable support, this study could not have been completed. We also thank Drs Angela Hoyos and Juan G. Piñeros for valuable input during the initial design of this study. Special thanks go to Maryellen Lane for Neonatal Resuscitation Program training. We thank Drs Claudia Granados and Juan Gabriel Ruiz, members of the safety review committee, and we thank Viviana Rodriguez for her excellent work as a data manager. Special thanks go to Dr Robert Cotton and Amanda Solis for reviewing the manuscript. Ms Rojas is a PhD candidate at Universidad Autonoma de Barcelona.

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Pediatrics 2009;123;137-142
DOI: 10.1542/peds.2007-3501