Original Investigation

Late Surfactant Administration in Very Preterm Neonates With Prolonged Respiratory Distress and Pulmonary Outcome at 1 Year of Age
A Randomized Clinical Trial

Jean-Michel Hascoët, MD; Jean-Charles Picaud, MD, PhD; Isabelle Ligi, MD; Thierry Blanc, MD; Francois Moreau, MD; Marie-Frederique Pinturier, MD; Véronique Zupan, MD; Isaura Guilhoto, MD; Isabelle R. M. Hamon, MD, PhD; Ceneric Alexandre, MD; Antoine Bouissou, MD; Laurent Storme, MD, PhD; Juliana Patkai, MD; Mickael Pomedio, MD; Mahmoud Rouabah, MD; Ludivine Coletto, MD; Rachel Vieux, MD, PhD

IMPORTANCE Although immature neonate survival has improved, there is an increased risk of developing bronchopulmonary dysplasia, leading to significant respiratory morbidity. Measures to reduce bronchopulmonary dysplasia are not always effective or have important adverse effects.

OBJECTIVE To evaluate the effect of late surfactant administration in infants with prolonged respiratory distress on ventilation duration, respiratory outcome at 36 weeks' postmenstrual age, and at 1 year postnatal age.

DESIGN, SETTING, AND PARTICIPANTS Double-blind randomized clinical trial at 13 level III French perinatal centers. Participants included 118 neonates at less than 33 weeks' gestation who still required mechanical ventilation on day 14 (SD, 2) with fraction of inspired oxygen of more than 0.30. All survivors were eligible for follow-up. We performed an intent-to-treat analysis.

INTERVENTIONS Infants received 200 mg/kg of poractant alfa (surfactant) or air after randomization. At 1 year, after parents' interview, infants underwent physical examination by pediatricians not aware of the randomization.

MAIN OUTCOMES AND MEASURES The duration of ventilation was the primary outcome. The combined outcome of death or bronchopulmonary dysplasia at 36 weeks' postmenstrual age and respiratory morbidity at 1 year of age were the main secondary outcome measures.

RESULTS Of the 118 infants who participated in the study, 65 (55%) were male. Fraction of inspired oxygen requirements dropped after surfactant, but not air, for up to 24 hours after instillation (0.36 [0.11] vs 0.43 [0.18]; $P < .005$). Severe bronchopulmonary dysplasia/death rates at 36 weeks' postmenstrual age were similar (27.1% vs 35.6%; $P = .32$). Less surfactant-treated infants needed rehospitalization for respiratory problems after discharge (28.3% vs 51.1%; $P = .03$); 39.5% vs 50% needed respiratory physical therapy ($P = .35$). No difference was observed for weight (7.8 [1.2] kg vs 7.6 [1.1] kg), height (69 [5] cm vs 69 [3] cm), and head circumference (44.4 [1.7] cm vs 44.2 [1.7] cm) measured at follow-up, nor for neurodevelopment outcome.

CONCLUSIONS AND RELEVANCE Late surfactant administration did not alter the early course of bronchopulmonary dysplasia. However, surfactant-treated infants had reduced respiratory morbidity prior to 1 year of age.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT01039285

JAMA Pediatr. doi:10.1001/jamapediatrics.2015.4617
Published online February 29, 2016.

Editorial

Supplemental content at jamapediatrics.com

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Jean-Michel Hascoët, MD, Department of Neonatology, Maternité Régionale Universitaire, Université de Lorraine, EA3450, 10 rue Dr Heydenreich, 54035 Nancy, France (j.hascoet@chru-nancy.fr).

Immature neonate survival has significantly improved, with advances in perinatal care such as prenatal use of corticosteroids,[1,2] continuous positive airway pressure at birth,[3-5] and early use of exogenous surfactant.[6] However, the cost of improved survival is an increased risk of developing bronchopulmonary dysplasia (BPD).[7] Bronchopulmonary dysplasia is responsible for chronic lung disease and abnormal neurodevelopment.[8,9] Different therapeutic approaches have been proposed for treating BPD including postnatal corticosteroids,[1,10] antioxidant treatments,[11] and various strategies of assisted ventilation that aim to reduce barotrauma or volutrauma.[12] However, some of these have been relatively ineffective and others may be related to long-term major adverse effects.[2,12]

Factors associated with severe BPD include the presence of cellular debris in distal airways,[13] cellular dysfunctions in type II pneumocytes,[14,15] episodes of edema and inflammatory bursts,[12,16] alterations in airway compliance, disorders in bronchomotor function,[17] impairments in pulmonary healing and growth,[12,18] and increased oxidative stress.[19] The application of mechanical ventilation alone alters surfactant and growth factor expression.[20] All these factors could theoretically respond to surfactant treatment.

The objectives of this study were to evaluate the effect of late surfactant administration at the age of first extubation in infants with severe respiratory distress that required prolonged invasive ventilation and to evaluate the effect of late surfactant administration on the respiratory outcome of the infants at 36 weeks' postmenstrual age (PMA) and 1 year of age.[21,22]

Key Points

Question: Could surfactant administration at 2 weeks of age in very preterm infants with prolonged respiratory distress reduce ventilation duration and respiratory morbidity?

Findings: In this randomized clinical trial, there was no difference in ventilation duration; there was a significant decrease in rehospitalization rate for respiratory problems after discharge within the first year postnatal age (28.3% vs 51.1%).

Meaning: Late surfactant administration is associated with better pulmonary outcome than controls at 1 year of age.

Methods

This prospective, randomized, controlled, double-blinded, multicenter trial was conducted in 13 level III French Perinatal Centers from December 2009 to November 2012. It was approved by the Comité de Protection des Personnes de Lorraine Ethics Committee (see study protocol in Supplement 1). Written consent from the parents or legal guardian was obtained before randomization.

Inclusion Criteria

Neonates were eligible if they were born before 33 weeks' gestation and still needed conventional mechanical ventilation or high-frequency oscillatory ventilation at 14 days of life (SD, 2) with a fraction of inspired oxygen (FiO_2) of more than 0.30 and/or an oxygenation index (FiO_2 multiplied by mean airway pressure per arterial oxygen pressure) of 8 or more for at least 6 hours (based on arterial or percutaneous blood gases and measured with a sensor in the postductal position).

Exclusion Criteria

Infants were excluded if they had an active infection, defined as a C-reactive protein (CRP) level of more than 30 mg/L (to convert to nanomoles per liter, multiply by 9.524), that was not controlled with an antibiotic treatment that targeted an identified microbe at the time of randomization; if they had undergone a surgical intervention within the past 72 hours; or if they presented with a disease (chromosomal or neurological) that might contraindicate extubation.

Blinding Procedure

A practitioner not involved in the child's care contacted the coordinator center and received the number of an opaque, sealed envelope available in the centers. The envelope contained the notification of the assigned treatment. According to the assignment, the practitioner proceeded to instill either poractant alfa (surfactant group) at 2.5 mL/kg (200 mg/kg) or the same volume of air (control group), without knowledge of the personnel (medical and nursing) involved in the child's care. Care was then continued according to the unit's routine without knowledge of the treatment allocation.

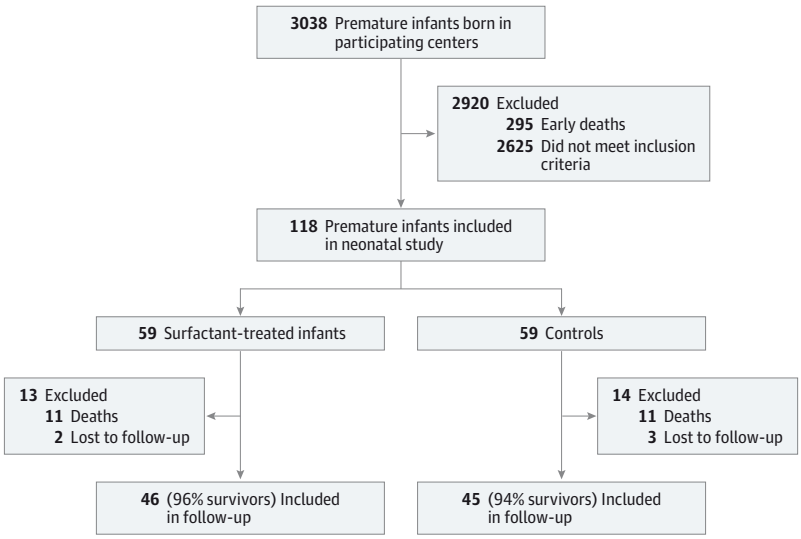
Measures of Outcome

The primary outcome was the time to first successful extubation. Predefined extubation criteria included: FiO_2 less than 0.30 for arterial oxygen percent saturation between 88% and 92% and partial pressure of carbon dioxide between 40 and 55 mm Hg for at least 6 hours. Extubation was considered successful when adequate spontaneous respiration was maintained for at least 72 hours. Criteria for reintubation included 6 episodes of apnea and/or bradycardia that required stimulation over a 6-hour period; 1 episode of apnea and/or bradycardia that required resuscitation with positive pressure; FiO_2 greater than 0.60; or partial pressure of carbon dioxide greater than 60 mm Hg for at least 6 hours.[3]

Hospital secondary outcomes included BPD or death at 36 weeks' PMA according to the Jobe and Bancalari definition.[16] We also recorded short-term changes in FiO_2 requirements after instillation of surfactant or air. Similarly, general inflammation, defined as CRP level of more than 10 mg/mL, was measured before and 48 hours after instillation. Finally, neonatal morbidities such as late-onset sepsis (defined as clinical deterioration, elevated CRP, and bacteria isolated in blood culture); cerebral intraventricular hemorrhage or ventricular dilatation; feeding tolerance; and necrotizing enterocolitis were evaluated.

Infants that remained intubated at 28 days of age had echocardiographic evaluation. Associated pulmonary hypertension was defined as the presence of tricuspid regurgitation and/or a ratio less than 0.54 of the time-to-peak velocity/

Figure 1. CURDYS Study Diagram Flow



right ventricular ejection time.[23-25] To treat associated pulmonary hypertension, 10 ppm inhaled nitric oxide (iNO) were added for 1 to 3 weeks, depending on weekly hemodynamics evaluations.

All surviving infants were eligible for follow-up at 1 year of age. After a parents' interview recording all events that occurred since discharge, the infants underwent complete physical examination by certified, trained pediatricians not aware of the randomization. Uses of health care resources were recorded, including rehospitalization for respiratory problems with the need for reintubation, invasive ventilation, and oxygen supplementation; corticosteroid use after discharge; outpatient visits for respiratory or any problem; and home chest physical therapy. Parents will remain blinded for randomization until the end of the follow-up scheduled at 7 years of age. Neurodevelopment was evaluated with selected items of the Brunet-Lezine test[26] including motor, coordination, language, and socialization subtests.

Permitted Associated Treatments

Hydrocortisone was allowed in cases of corticotropic axis immaturity, and short-term betamethasone treatment was allowed at the sole discretion of the clinical team in charge of the infant for extubation.[10]

Statistics

Sample size was calculated based on a previous study with a neonate population similar to the population of this study.[27] We considered a difference of 10 days of mechanical ventilation between the groups to be clinically significant in a 2-sided test with an α risk of 5% and a power of 90%. The calculated number of patients required was at least 43 per group (Power and Precision software, 2001; Biostat Ed). Considering an estimated 20% risk of losing patients to follow-up, a sample size of at least 50 children per group was expected to be sufficient. We performed an intent-to-treat analysis.

General neonate characteristics were compared between groups with a χ^2 test for categorical variables and a comparison of means test for continuous variables. A *t* test was used to compare the mean duration of ventilation between groups and among subgroups of different ages (in days). A χ^2 test (or a Fisher exact test, when appropriate) was used to compare percentages, and a *t* test (or a rank test, when necessary) was used to compare means of quantitative variables between groups. Mann-Whitney *U* test was used for neurodevelopment subscores comparison at 1 year of age. Analyses were performed with SAS software, version 9.1 (SAS Institute Inc).

Results

Patients

Thirteen centers included 118 infants from December 2009 to November 2012 (**Figure 1**). They and their mothers were similar in perinatal characteristics. There was no significant pathology of pregnancy in only 9 (15%) vs 7 (12%) mothers of infants in the control (n = 59) vs surfactant (n = 59) groups, respectively (*P* = .59) (**Table 1**). Early-onset sepsis was present in 25 (44%) vs 26 (41%) infants (*P* = .58). All infants had received Curosurf for respiratory distress prophylaxis before 1 hour of life. There were no differences in respiratory support or FiO_2 at randomization.

The groups were similar in the detection and treatment of associated pulmonary hypertension. In the control vs surfactant groups, respectively, 27 vs 20 infants received iNO (*P* = .20) at mean (SD) 28.5 (0.5) days vs 28.7 (1.9) days, for 11.1 (9.3) days vs 12.3 (4.9) days.

Primary Outcome

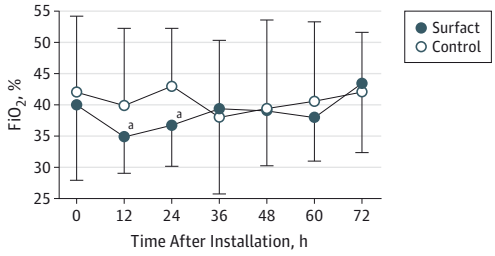
The mean (SD) age at first successful extubation was not different between groups (control, 38.3 [18.5] days vs surfactant, 35.7 [20.0] days; *P* = .29). All extubation criteria were

Table 1. Perinatal Characteristics of Mothers and Neonates

Characteristic	Poractant Alfa (n = 59)	Control (n = 59)
Maternal characteristics, No. (%)		
Nephropathy of pregnancy	17 (29)	18 (31)
Premature rupture of membranes	21 (36)	14 (24)
Oligohydramnios	15 (26)	11 (19)
Chorioamniotitis	5 (8)	5 (8)
Other infection at delivery	5 (8)	6 (10)
Diabetes	2 (3)	4 (7)
Prenatal steroids (any)	53 (89)	49 (83)
Steroid maturation (complete)	38 (65)	38 (65)
Cesarean section	27 (46)	34 (57)
Infants characteristics		
Gestational age, mean (SD, range), wk	26.2 (1.5, 24-31)	26.6 (1.3, 23-30)
Birth weight, mean (SD), g	814 (157)	770 (174)
Severe IUGR (<3rd percentile)	9 (15)	8 (14)
Male, No. (%)	33 (56)	32 (54)
CRIB score, mean (SD, median)	5.3 (2.8, 5)	6.0 (3.0, 7)
Apgar scores (medians: 1/5 min)	4/6	3.5/7
Age at randomization, mean (SD), d	14.6 (1.3)	14.4 (1.3)
FiO_2 at randomization, mean (SD)	0.40 (0.13)	0.42 (0.15)
Conventional mechanical ventilation, No.	28	33
Airway pressure in cm H_2O, mean (SD)	10.4 (2.0)	10.1 (2.7)
High frequency oscillation, No.	31	26
Airway pressure in cm H_2O, mean (SD)	13.0 (2.3)	13.5 (1.8)

Abbreviations: CRIB, Clinical Risk Index for Babies; FiO_2, fraction of inspired oxygen; IUGR, interuterine growth restriction.

Figure 2. Changes in Fraction of Inspired Oxygen (FiO_2) Requirements for 72 Hours After Surfactant (Surfact) or Air (Control) Instillation (Mean [SD])



[a] $P < .05$.

present before extubation in 26.5% and 26.8% ($P = .98$), and extubation failed at least once in 22 (37.3%) control and 18 (30.3%) surfactant infants ($P = .45$). On day 28, 17 (31%) control and 23 (41%) surfactant infants ($P = .27$) were extubated.

In-Hospital Secondary Outcomes

After instillation, FiO_2 requirements dropped significantly in the surfactant group compared with the control group for 24 hours, but after 36 hours, the groups no longer showed a difference (**Figure 2**). No adverse events were associated with surfactant administration. No difference was observed in inflammation between groups; CRP was greater than 10 mg/mL in 3 control and 7 surfactant infants before instillation, and in 7 control and 6 surfactant infants 48 hours after instillation. Negative baseline CRP rose to more than 10 mg/mL at 48 hours in 6 control and 1 surfactant infants.

Eleven infants died in each group. Bronchopulmonary dysplasia severity levels were similar: 8 vs 3 mild, 30 vs 40 moderate, and 21 vs 16 severe BPD/death for control and surfactant infants, respectively ($P = .11$). The rate of the composite outcome, severe BPD, or death were not different at 36 weeks' PMA (**Table 2**). Of note, infants who received iNO required respiratory support longer in the control (median, 82 days; range, 41-191 days) than in the surfactant group (median, 65 days; range, 38-263 days; $P = .15$). Three infants that had received iNO died in each group.

Both groups had high rates of late-onset sepsis. Infants in the surfactant group had better feeding tolerance with less necrotizing enterocolitis and shorter durations of hospitalization among survivors (Table 2). The 2 groups were not significantly different in other morbidities.

1-Year Follow-up Outcome

Follow-up was performed at a median of 12.6 months (range, 10.2-15.2 months) vs 12.4 months (range, 10.1-15.9 months) postnatal age ($P = .44$) in the control and surfactant groups, respectively. Parents' education and family social status were similar in the 2 groups (eTable in Supplement 2). There was no difference for the rate of passive smoking exposure (12 of 37 vs 12 of 40, $P = .82$ in the control and surfactant groups, respectively). More infants were kept at home during the first year of life in the control group, while more infants were kept by a childminder or attended a daycare in the surfactant group (eTable in Supplement 2). Nevertheless, fewer surfactant-treated infants needed rehospitalization for respiratory problems after discharge: 13 surfactant-treated infants (28.3%) vs 23 control-group infants (51.1%) ($P = .03$), with a median of 1 (IQR, 1-3) vs 2 (IQR, 1-8) episodes for the infants needing rehospitalization. There was no difference for infants who had received iNO in the neonatal period: 15 of 24 vs 9 of 17 ($P = .54$) needed at least 1 rehospitalization after discharge in the control and surfactant groups, respectively. Other follow-up data are displayed in **Table 3**.

Discussion

This study showed that among very premature infants with severe respiratory distress, late surfactant administration did not significantly shorten the time to extubation compared with controls. The surfactant group of infants had 2.5 days shorter intubations and 10% more extubations on day 28, but that was not significant. Also, we observed no significant difference in the combined outcome of death/BPD between groups at 36 weeks' PMA. However, at 1 year postnatal age, formerly sick, very premature infants treated with

Table 2. Neonatal Outcome

Study Group	No. (%) Poractant Alfa (n = 59)	No. (%) Control (n = 59)	OR (95% CI)	*P* Value
Mortality	11 (18.6)	11 (18.6)	1 [Reference]	>.99
Severe BPD or death	16 (27.1)	21 (35.6)	0.673 (0.308-1.474)	.32
Discharged home on oxygen	13 (28)	10 (22)	0.725 (0.280-1.879)	.51
Total days of FiO_2 in survivors, mean (SD), d	105 (35)	108 (46)		.76
Hospitalization in survivors, mean (SD), d	117 (30)	124 (40)		.08
Postnatal steroids in survivors	51 (87)	54 (92)	0.532 (0.145-1.954)	.53
Late-onset sepsis	55 (93)	56 (95)	0.737 (0.158-3.445)	.70
Receiving full feeds on day 28	59 (98)	50 (85)	9.362 (1.130-77.634)	.04
Necrotizing enterocolitis	5 (8)	15 (25)	0.272 (0.092-0.806)	.02
Patent ductus arteriosus	40 (68)	42 (71)	0.852 (0.389-1.868)	.69
Intraventricular hemorrhage in survivors	19 (39)	17 (35)	1.195 (0.523-2.732)	.67
Cerebral ventricular dilatation in survivors	3 (6)	9 (19)	0.289 (0.073-1.142)	.06

Abbreviations: BPD, bronchopulmonary dysplasia; FiO_2, fraction of inspired oxygen; OR, odds ratio.

Table 3. Follow-up at 1 Year Postnatal Age

Study Group	Mean (SD) Poractant Alfa	Mean (SD) Controls	OR (95% CI)	*P* Value
No. children (% survivors)	46 (96)	45 (94)		.65
Corrected age at evaluation, mo	9.5 (1.5)	9.6 (1.1)		.69
Weight, kg	7.8 (1.2)	7.6 (1.1)		
Corrected *z* score	−0.89 (1.05)	−1.14 (1.09)		.38
Length, cm	69.4 (5.2)	68.7 (3.5)		
Corrected *z* score	−1.12 (1.47)	−1.44 (1.26)		.46
Head circumference, cm	44.4 (1.7)	44.2 (1.7)		.54
Children, No. (%)				
Rehospitalized for respiratory problems	13 (28.3)	23 (51.1)	0.377 (0.158-0.898)	.03
Requiring CMV	1 (2)	5 (11)	0.178 (0.020-1.587)	.12
Requiring 02 since discharge	7 (15)	10 (22)	0.628 (0.216-1.828)	.39
With steroids since discharge	21 (45)	27 (60)	0.551 (0.235-1.290)	.17
Outpatient visits for respiratory problems, No. (%)	26 (57)	26 (56)	1.040 (0.454-2.380)	.93
Chest physical therapy, No. (%)	18 (39)	23 (50)	0.654 (0.279-.530)	.33
Global neurodevelopment (% maximum score)	73 (21)	74 (21)		.85
Subscore				
Motor	74 (36)	72 (38)		.83
Coordination	92 (26)	97 (10)		.18
Language	76 (30)	78 (27)		.71
Socialization	51 (35)	50 (35)		.94

Abbreviations: CMV, conventional mechanical ventilation; OR, odds ratio.

late surfactant needed significantly less rehospitalization for pulmonary problems than infants in the control group after discharge (OR, 0.377 [95% CI, 0.158-0.898], *P* = .03). We speculate that the absence of significant differences at extubation or 36 weeks' PMA may be caused by too-short time periods for adequate evaluation. In accordance with the National Institutes of Health recommendation that respiratory health care use and respiratory symptoms at 1 year of age are more meaningful indicators of respiratory morbidity than the 36 weeks' PMA evaluation,[21,22] our results at 1 year might better reflect our infants' respiratory outcome. Of note, the clinical status of the infants at discharge suggests a difference in illness severity between the groups. Surfactant infants had significantly less necrotizing enterocolitis and earlier full enteral feeding; they needed slightly less postnatal steroids and were discharged about 1 week earlier than controls. The numbers are too small to reach statistical significance, but it suggests that surfactant-treated infants had a better clinical status after discharge. However, we cannot exclude unidentified confounding factors leading to the same evolution.

Tremblay et al[28] recalled that, owing to lung heterogeneity, mechanical ventilation is associated with alveolar distension in very premature infants, leading to severe lung injury. Mechanical ventilation prevents healing,[18] and extubation is indeed an issue in these vulnerable infants. Digeronimo et al[20] showed that mechanical ventilation could downregulate surfactant protein expression. In a randomized trial by Keller et al,[29] 85 very premature infants were administered up to 5 doses of surfactant from 7 to 15 days post natal with iNO compared with iNO alone. They showed that low surfactant protein values increased after surfactant administration, with an improvement in the clinical status of the infants, but the effects waned after 1 day.[29] In a retrospective analysis of 126 infants, Katz et al[30] evaluated 25 infants who received 1 repeated course of surfactant therapy for respiratory failure after 6 days. They found that 70% of them had significant improvement in their lung disease up to 48 hours after instillation. Those results are consistent with our study. However, because of the advances in perinatal care, adding the requirement of at least 30% oxygen to invasive ventilation to prevent the inclusion of infants on ventilation for other reasons than pulmonary disease led to a selected subgroup of about 5% of the newborns presenting with prolonged pulmonary disease. In the study used for sample size calculation,[27] 16% of the infants had more than 14 days of ventilation and 75% developed BPD. Because all our infants had BPD or died at 36 weeks' PMA, we only observed a nonsignificant difference, in favor of surfactant, for severe BPD or death at 36 weeks' PMA (OR, 0.673 [95% CI, 0.308-1.474]).

More than 40% of infants in each group were treated for inflammation, giving rise to a suspicion of materno-fetal infection. Paananen et al[31] studied 128 very premature infants and found that infants with inflammation and high concentrations of inflammatory cytokines in cord blood were at high risk of BPD. Schneibel et al[32] examined the tracheal aspirates of 27 very low-birth-weight neonates and showed that high levels of inflammatory mediators increased the risk of developing BPD. In addition, Marshall et al[33] investigated chronic lung disease risk factors among 1224 very low-birth-weight infants. They showed that, among 423 infants who received more than 48 hours of ventilation, nosocomial infection was significantly associated with an increased risk of BPD.[33]

In our study, more than 90% of the infants presented with late-onset sepsis. This is consistent with the status of the highly vulnerable group of patients included in the study and the overall rate of late-onset sepsis, ranging from 14% to 24% in the participating centers for infants below 33 weeks' gestation. Groneck et al[12] demonstrated an association between pulmonary inflammation and increased microvascular permeability during BPD development, which is consistent with our study.

Two studies raised concern that poractant alfa might contribute to elevated CRP.[34,35] el Hanache et al[34] retrospectively studied 150 premature infants treated with or without surfactant, and mean CRP rose significantly in infants treated with poractant alfa. However, the groups were not comparable at baseline, and the authors did not report more infants with positive CRP, only a higher mean CRP in the treated group, which is not an appropriate indicator.[34] Kukkonen et al[35] found that 45% of infants treated with poractant alfa vs 12% treated with Exosurf had CRP values above the threshold for risk of infection. However, some infants had documented infections, and no blood control had been obtained before instillation. Therefore, no conclusion could be drawn from that study. In our randomized study, the groups were not different either before or 48 hours after instillation. Therefore, a direct inflammatory effect of poractant alfa is highly unlikely.

We had hypothesized that iNO might be synergistic with surfactant. Vascular abnormalities associated with BPD may lead to pulmonary arterial hypertension.[23] We and others have shown that iNO may be used safely in neonates for prevention[27] or treatment of BPD.[24,36] Nitric oxide does not have any adverse effects on surfactant,[37] but evidence for iNO efficacy remains insufficient to recommend its use for BPD. However, it may be considered when respiratory distress is associated with pulmonary hypertension.[23,29,36] We found that when iNO was added to surfactant in cases of associated pulmonary hypertension, the median duration of respiratory support was 17 days shorter than when iNO was applied without surfactant. However, our study was not powered to answer that question. Other studies have shown that combined iNO and surfactant decreased morbidity at follow-up,[38] despite no significant benefit at 36 weeks' PMA. In our study, we did not find a significant effect of iNO on the respiratory outcome at 1 year postnatal age.

Our study had limitations. First, the extubation criteria were not strictly fulfilled for all infants. Practitioners sometimes judged the infants ready for extubation even though they did not meet the protocol criteria. This discrepancy may have been caused by the predefined study criteria that had been validated for acute situations but not for chronic respiratory disease.[3] Nevertheless, the groups were not significantly different in the number of extubation failures. Thus, this protocol violation was unlikely to have biased the results. Second, we had intended to restrain postnatal corticosteroid use to improve the evaluation of the effects of surfactant. Hydrocortisone was only allowed when infants exhibited corticotropic axis immaturity and short-term betamethasone treatment for extubation support only.[10] However, about 90% of the infants eventually received postnatal steroid throughout the neonatal period. This high rate of corticosteriod use may have blunted an effect of surfactant, despite the lack of difference in steroid use between the 2 groups. Finally, despite most confounding factors for respiratory morbidity, such as parents' education, family social status, or passive smoking, exposure was similar between the groups, although more infants were kept by a childminder or attended a daycare in the surfactant group. Because an increased incidence in respiratory infections and morbidity is associated with daycare attendance,[39] this discrepancy in favor of the control group may have blunted an effect of surfactant.

Conclusions

Late surfactant administration showed an acceptable safety profile and was associated with a better pulmonary outcome than controls at 1 year of age. Evaluation at 36 weeks' PMA or

discharge did not show a significant improvement, but because the infants involved in the study had a severe prolonged pulmonary disease at baseline, these times may have been too early to appreciate a significant effect. However, we cannot exclude that other clinical factors may also be responsible for part of the observed differences.

ARTICLE INFORMATION

Accepted for Publication: February 29, 2016.

Published Online: February 29, 2016. doi:10.1001/jamapediatrics.2015.4617.

Author Affiliations: Maternite Regionale Universitaire, EA 3450 Devah, Université de Lorraine, Nancy, France (Hascoët, Hamon, Rouabah); Hôpital de la Croix-Rousse, Hospices Civils de Lyon, Lyon, France (Picaud, Coletto); Assistance Publique-Hopitaux Marseille, Marseille, France (Ligi); Centre Hospitalier Universitaire Rouen, Rouen, France (Blanc); Centre Hospitalier Universitaire Amiens, Amiens, France (Moreau); Centre Hospitalier Montreuil, Montreuil, France (Pinturier); Assistance Publique-Hopitaux Clamart, Clamart, France (Zupan); Centre Hospitalier Arras, Arras, France (Guilhoto); Centre Hospitalier Universitaire Caen, Caen, France (Alexandre); Centre Hospitalier Universitaire Tours, Tours, France (Bouissou); Centre Hospitalier Universitaire Lille, Lille, France (Storme); Assistance Publique-Hopitaux Paris Port Royal, Paris, France (Patkai); Centre Hospitalier Universitaire Reims, Reims, France (Pomedio); Maternite Regionale Universitaire, EA 4360 APEMAC, Université de Lorraine, Nancy, France (Vieux).

Author Contributions: Dr Hascoët had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Hascoët.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Hascoët.
Critical revision of the manuscript for important intellectual content: Hascoët, Picaud, Ligi, Blanc, Moreau, Pinturier, Zupan, Guilhoto, Hamon, Alexandre, Bouissou, Storme, Patkai, Roubah, Coletto, Vieux.
Statistical analysis: Vieux.
Obtaining funding: Hascoët.
Administrative, technical, or material support: Hascoët, Picaud, Moreau, Pinturier, Zupan, Hamon, Roubah, Coletto, Vieux.
Study supervision: Hascoët, Hamon.

Conflict of Interest Disclosures: None reported.

Funding/Support: The study was supported by the French Ministry of Health (grant PHRC 2011-2013), an unrestricted grant from Chiesi SA, the Maternité Régionale Universitaire, and unrestricted grants from the nonprofit associations Association d'aide aux Insuffisants Respiratoires de Lorraine and Association pour la Promotion de la Recherche et de l'Enseignement pour les Soins aux Nouveau-nés.

Role of the Funder/Sponsor: The French Ministry of Health, the Maternité Régionale Universitaire, Association d'aide aux Insuffisants Respiratoires de Lorraine, and Association pour la Promotion de la Recherche et de l'Enseignement pour les Soins aux Nouveau-nés did not have any role in the design and conduct the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. Chiesi SA did not have any role in the design and conduct the study; collection, management, analysis, and interpretation of the data; preparation or approval of the manuscript; and decision to submit the manuscript for publication, but they reviewed the manuscript for their information and did not propose any change in the text.

Additional Contributions: We thank Marie-Christine Buchweiller, Sabine Guignon (Research Nurses, Maternite Regionale Universitaire, Centre Hospitalier Universitaire Nancy), and Anne-Fleur André (Research Technician, Maternite Regionale Universitaire, Centre Hospitalier Universitaire Nancy) for data monitoring and management. We thank Diomande Douty, MD (Clamart), and Fouad Elie Haddad, MD (Nancy), for active participation in collecting data and monitoring files. Finally, we thank Olivier Claris (Centre Hospitalier Universitaire Nancy Lyon) and Thierry Debillon (Centre Hospitalier Universitaire Nancy Grenoble) for active participation in the steering committee. None of these individuals received compensation for their work.

REFERENCES

1. LeFlore JL, Salhab WA, Broyles RS, Engle WD. Association of antenatal and postnatal dexamethasone exposure with outcomes in extremely low birth weight neonates. *Pediatrics*. 2002;110(2, pt 1):275-279.

2. Hamon I, Hascoet JM. Perinatal corticotherapy: updates [in French]. *J Gynecol Obstet Biol Reprod (Paris)*. 2001;30(6)(suppl):S50-S53.

3. Morley CJ, Davis PG, Doyle LW, Brion LP, Hascoet JM, Carlin JB; COIN Trial Investigators. Nasal CPAP or intubation at birth for very preterm infants. *N Engl J Med*. 2008;358(7):700-708.

4. Sandri F, Plavka R, Ancora G, et al; CURPAP Study Group. Prophylactic or early selective surfactant combined with nCPAP in very preterm infants. *Pediatrics*. 2010;125(6):e1402-e1409.

5. Finer NN, Carlo WA, Walsh MC, et al; SUPPORT Study Group of the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Early CPAP versus surfactant in extremely preterm infants. *N Engl J Med*. 2010;362(21):1970-1979.

6. Halliday HL. Recent clinical trials of surfactant treatment for neonates. *Biol Neonate*. 2006;89(4):323-329.

7. Parker RA, Lindstrom DP, Cotton RB. Improved survival accounts for most, but not all, of the increase in bronchopulmonary dysplasia. *Pediatrics*. 1992;90(5):663-668.

8. Redline RW, Wilson-Costello D, Hack M. Placental and other perinatal risk factors for chronic lung disease in very low birth weight infants. *Pediatr Res*. 2002;52(5):713-719.

9. Davis PG, Thorpe K, Roberts R, Schmidt B, Doyle LW, Kirpalani H; Trial Indomethacin Prophylaxis in Preterms Investigators. Evaluating "old" definitions for the "new" bronchopulmonary dysplasia. *J Pediatr*. 2002;140(5):555-560.

10. Brozanski BS, Jones JG, Gilmour CH, et al. Effect of pulse dexamethasone therapy on the incidence and severity of chronic lung disease in the very low birth weight infant. *J Pediatr*. 1995;126(5, pt 1):769-776.

11. Frank L, Sosenko IR. Failure of premature rabbits to increase antioxidant enzymes during hyperoxic exposure: increased susceptibility to pulmonary oxygen toxicity compared with term rabbits. *Pediatr Res*. 1991;29(3):292-296.

12. Groneck P, Götze-Speer B, Oppermann M, Eiffert H, Speer CP. Association of pulmonary inflammation and increased microvascular permeability during the development of bronchopulmonary dysplasia: a sequential analysis of inflammatory mediators in respiratory fluids of high-risk preterm neonates. *Pediatrics*. 1994;93(5):712-718.

13. Pierce MR, Bancalari E. The role of inflammation in the pathogenesis of bronchopulmonary dysplasia. *Pediatr Pulmonol*. 1995;19(6):371-378.

14. Moya FR, Montes HF, Thomas VL, Mouzinho AM, Smith JF, Rosenfeld CR. Surfactant protein A and saturated phosphatidylcholine in respiratory distress syndrome. *Am J Respir Crit Care Med*. 1994;150(6 Pt 1):1672-1677.

15. Janssen DJ, Carnielli VP, Cogo PE, et al. Surfactant phosphatidylcholine half-life and pool size measurements in premature baboons developing bronchopulmonary dysplasia. *Pediatr Res*. 2002;52(5):724-729.

16. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. *Am J Respir Crit Care Med*. 2001;163(7):1723-1729.

17. Albertine KH, Jones GP, Starcher BC, et al. Chronic lung injury in preterm lambs: disordered respiratory tract development. *Am J Respir Crit Care Med*. 1999;159(3):945-958.

18. Jobe AH, Ikegami M. Mechanisms initiating lung injury in the preterm. *Early Hum Dev*. 1998;53(1):81-94.

19. Matalon S, Hu P, Ischiropoulos H, Beckman JS. Peroxynitrite inhibition of oxygen consumption and ion transport in alveolar type II pneumocytes. *Chest*. 1994;105(3)(suppl):74S.

20. Digeronimo RJ, Mustafa SB, Ryan RM, Sternberg ZZ, Ashton DJ, Seidner SR. Mechanical ventilation down-regulates surfactant protein A and keratinocyte growth factor expression in premature rabbits. *Pediatr Res*. 2007;62(3):277-282.

21. Walsh MC, Szefler S, Davis J, et al. Summary proceedings from the bronchopulmonary dysplasia group. *Pediatrics*. 2006;117(3, pt 2):S52-S56.

22. Maitre NL, Ballard RA, Ellenberg JH, et al; Prematurity and Respiratory Outcomes Program. Respiratory consequences of prematurity: evolution of a diagnosis and development of a comprehensive approach. *J Perinatol*. 2015;35(5):313-321.

23. Su BH, Watanabe T, Shimizu M, Yanagisawa M. Doppler assessment of pulmonary artery pressure in neonates at risk of chronic lung disease. *Arch Dis Child Fetal Neonatal Ed*. 1997;77(1):F23-F27.

24. Clark PL, Ekekezie II, Kaftan HA, Castor CA, Truog WE. Safety and efficacy of nitric oxide in chronic lung disease. *Arch Dis Child Fetal Neonatal Ed*. 2002;86(1):F41-F45.

25. Skinner JR, Boys RJ, Heads A, Hey EN, Hunter S. Estimation of pulmonary arterial pressure in the newborn: study of the repeatability of four Doppler echocardiographic techniques. *Pediatr Cardiol*. 1996;17(6):360-369.

26. Brunet O, Lézine I, Josse D, et al. *Brunet-Lézine Révise: Echelle de Developpement Psychomoteur de la Petite Enfance: Manuel BLR-C*. Paris, France: Editions et Applications Psychologiques; 2001.

27. Hascoët JM, Fresson J, Claris O, et al. The safety and efficacy of nitric oxide therapy in premature infants. *J Pediatr*. 2005;146(3):318-323.

28. Tremblay LN, Slutsky AS. Pathogenesis of ventilator-induced lung injury: trials and tribulations. *Am J Physiol Lung Cell Mol Physiol*. 2005;288(4):L596-L598.

29. Keller RL, Merrill JD, Black DM, et al. Late administration of surfactant replacement therapy increases surfactant protein-B content: a randomized pilot study. *Pediatr Res*. 2012;72(6):613-619.

30. Katz LA, Klein JM. Repeat surfactant therapy for postsurfactant slump. *J Perinatol*. 2006;26(7):414-422.

31. Paananen R, Husa AK, Vuolteenaho R, Herva R, Kaukola T, Hallman M. Blood cytokines during the perinatal period in very preterm infants: relationship of inflammatory response and bronchopulmonary dysplasia. *J Pediatr*. 2009;154(1):39-43.e3.

32. Schneibel KR, Fitzpatrick AM, Ping XD, Brown LAS, Gauthier TW. Inflammatory mediator patterns in tracheal aspirate and their association with bronchopulmonary dysplasia in very low birth weight neonates. *J Perinatol*. 2013;33(5):383-387.

33. Marshall DD, Kotelchuck M, Young TE, Bose CL, Kruyer L, O'Shea TM; North Carolina Neonatologists Association. Risk factors for chronic lung disease in the surfactant era: a North Carolina population-based study of very low birth weight infants. *Pediatrics*. 1999;104(6):1345-1350.

34. el Hanache A, Gourrier E, Karoubi P, Merbouche S, Mouchnino G, Leraillez J. Modification of C-reactive protein after instillation of natural exogenous surfactants [Modification de la protéine C réactive après instillation de surfactant exogène naturel in French]. *Arch Pediatr*. 1997;4(1):27-31.

35. Kukkonen AK, Virtanen M, Järvenpää AL, Pokela ML, Ikonen S, Fellman V. Randomized trial comparing natural and synthetic surfactant: increased infection rate after natural surfactant? *Acta Paediatr*. 2000;89(5):556-561.

36. Ballard RA, Truog WE, Cnaan A, et al; NO CLD Study Group. Inhaled nitric oxide in preterm infants undergoing mechanical ventilation. *N Engl J Med*. 2006;355(4):343-353.

37. Ballard PL, Merrill JD, Truog WE, et al. Surfactant function and composition in premature infants treated with inhaled nitric oxide. *Pediatrics*. 2007;120(2):346-353.

38. Davis JM, Parad RB, Michele T, Allred E, Price A, Rosenfeld W; North American Recombinant Human CuZnSOD Study Group. Pulmonary outcome at 1 year corrected age in premature infants treated at birth with recombinant human CuZn superoxide dismutase. *Pediatrics*. 2003;111(3):469-476.

39. de Hoog MLA, Venekamp RP, van der Ent CK, et al. Impact of early daycare on healthcare resource use related to upper respiratory tract infections during childhood: prospective WHISTLER cohort study. *BMC Med*. 2014;12:107.