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To cite this version:


HAL Id: hal-01714378
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Submitted on 21 Feb 2018

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

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IMIMPORTANCE 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

Published online February 29, 2016.

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Attachments

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are 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: FiO2 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; FiO2 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 FiO2 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/
right ventricular ejection time. 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 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.

Statistics
Sample size was calculated based on a previous study with a neonate population similar to the population of this study. 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 χ² 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 χ² 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 sub-scores 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 FiO₂ 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
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
latesurfactant 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.

Table 2. Neonatal Outcome

<table>
<thead>
<tr>
<th>Study Group</th>
<th>No. (%)</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>Poractant Alfa (n = 59)</td>
<td>Control (n = 59)</td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>11 (18.6)</td>
<td>11 (18.6)</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Severe BPD or death</td>
<td>16 (27.1)</td>
<td>21 (35.6)</td>
<td>0.673 (0.308-1.474)</td>
</tr>
<tr>
<td>Discharged home on oxygen</td>
<td>13 (28)</td>
<td>10 (22)</td>
<td>0.725 (0.280-1.879)</td>
</tr>
<tr>
<td>Total days of FiO2 in survivors, mean (SD), d</td>
<td>105 (35)</td>
<td>108 (46)</td>
<td>.76</td>
</tr>
<tr>
<td>Hospitalization in survivors, mean (SD), d</td>
<td>117 (30)</td>
<td>124 (40)</td>
<td>.08</td>
</tr>
<tr>
<td>Postnatal steroids in survivors</td>
<td>51 (87)</td>
<td>54 (92)</td>
<td>0.532 (0.145-1.954)</td>
</tr>
<tr>
<td>Late-onset sepsis</td>
<td>55 (93)</td>
<td>56 (95)</td>
<td>0.737 (0.158-3.445)</td>
</tr>
<tr>
<td>Receiving full feeds on day 28</td>
<td>59 (98)</td>
<td>50 (85)</td>
<td>9.362 (1.130-77.634)</td>
</tr>
<tr>
<td>Necrotizing enterocolitis</td>
<td>5 (8)</td>
<td>15 (25)</td>
<td>0.272 (0.092-0.806)</td>
</tr>
<tr>
<td>Patent ductus arteriosus</td>
<td>40 (68)</td>
<td>42 (71)</td>
<td>0.852 (0.389-1.868)</td>
</tr>
<tr>
<td>Intraventricular hemorrhage in survivors</td>
<td>19 (39)</td>
<td>17 (35)</td>
<td>1.195 (0.523-2.732)</td>
</tr>
</tbody>
</table>

Abbreviations: BPD, bronchopulmonary dysplasia; FiO2, fraction of inspired oxygen; OR, odds ratio.

Table 3. Follow-up at 1 Year Postnatal Age

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Mean (SD)</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. children (% survivors)</td>
<td>Poractant Alfa</td>
<td>Controls</td>
<td></td>
</tr>
<tr>
<td>Corrected age at evaluation, mo</td>
<td>9.5 (1.5)</td>
<td>9.6 (1.1)</td>
<td>.69</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>7.8 (1.2)</td>
<td>7.6 (1.1)</td>
<td></td>
</tr>
<tr>
<td>Corrected z score</td>
<td>−0.89 (1.05)</td>
<td>−1.14 (1.09)</td>
<td>.38</td>
</tr>
<tr>
<td>Length, cm</td>
<td>69.4 (5.2)</td>
<td>68.7 (3.5)</td>
<td></td>
</tr>
<tr>
<td>Corrected z score</td>
<td>−1.12 (1.47)</td>
<td>−1.44 (1.26)</td>
<td>.46</td>
</tr>
<tr>
<td>Head circumference, cm</td>
<td>44.4 (1.7)</td>
<td>44.2 (1.7)</td>
<td>.54</td>
</tr>
<tr>
<td>Children, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rehospitalized for respiratory</td>
<td>13 (28.3)</td>
<td>23 (51.1)</td>
<td>.03</td>
</tr>
<tr>
<td>problems</td>
<td></td>
<td>0.377 (0.158-0.898)</td>
<td></td>
</tr>
<tr>
<td>Requiring 02 CMV</td>
<td>1 (2)</td>
<td>5 (11)</td>
<td>.12</td>
</tr>
<tr>
<td>Requiring O2 since discharge</td>
<td>7 (15)</td>
<td>10 (22)</td>
<td>.39</td>
</tr>
<tr>
<td>With steroids since discharge</td>
<td>21 (45)</td>
<td>27 (60)</td>
<td>.17</td>
</tr>
<tr>
<td>Outpatient visits for respiratory</td>
<td>26 (57)</td>
<td>26 (56)</td>
<td>.93</td>
</tr>
<tr>
<td>problems, No. (%)</td>
<td></td>
<td>1.040 (0.454-2.380)</td>
<td></td>
</tr>
<tr>
<td>Chest physical therapy, No. (%)</td>
<td>18 (39)</td>
<td>23 (50)</td>
<td>.33</td>
</tr>
<tr>
<td>Subscore</td>
<td></td>
<td>0.654 (0.279-1.290)</td>
<td>.33</td>
</tr>
<tr>
<td>Global neurodevelopment (% maximum</td>
<td>73 (21)</td>
<td>74 (21)</td>
<td>.85</td>
</tr>
<tr>
<td>score)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motor</td>
<td>74 (36)</td>
<td>72 (38)</td>
<td>.83</td>
</tr>
<tr>
<td>Coordination</td>
<td>92 (26)</td>
<td>97 (10)</td>
<td>.18</td>
</tr>
<tr>
<td>Language</td>
<td>76 (30)</td>
<td>78 (27)</td>
<td>.71</td>
</tr>
<tr>
<td>Socialization</td>
<td>51 (35)</td>
<td>50 (35)</td>
<td>.94</td>
</tr>
</tbody>
</table>

Abbreviations: CMV, conventional mechanical ventilation; OR, odds ratio.
Tremblay et al.28 recalled that, owing to lung heterogeneity, mechanical ventilation is associated with alveolar distortion in very premature infants, leading to severe lung injury. Mechanical ventilation prevents healing,18 and extubation is indeed an issue in these vulnerable infants. DiGeromino et al.20 showed that mechanical ventilation could down-regulate 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. Groene 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.22 We and others have shown that iNO may be used safely in neonates for prevention27 or treatment of BPD.24,36 Nitric oxide does not have any adverse effects on surfactant,27 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 corticotropin axis immaturity and short-term betamethasone treatment for extubation support only.30 However, about 90% of the infants eventually received postnatal steroid throughout the neonatal period. This high rate of corticosteroid 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.

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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, Guillotho, Hamon, Alexandre, Bouissou, Storme, Patka, Rouabah, Coletto, Vieux.

Statistical analysis: Vieux.

Obtaining funding: Hascoët.

Administrative, technical, or material support: Hascoët, Picaud, Moreau, Pinturier, Zupan, Hamon, Rouabah, 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 2010-2013), 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 of 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 Guigonon (Research Nurses, Maternité Régionale Universitaire, Centre Hospitalier Universitaire Nancy), and Anne-Fleur André (Research Technician, Maternité Régionale 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 Grenoble) for active participation in the steering committee. None of these individuals received compensation for their work.

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