Randomized Controlled Trial of Exogenous Surfactant for the Treatment of Hyaline Membrane Disease

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ABSTRACT. We conducted a prospective, randomized, unblinded, controlled trial of exogenous bovine surfactant (surfactant TA) in premature infants requiring ventilator support for the treatment of severe hyaline membrane disease. Forty-one low birth weight infants with severe hyaline membrane disease were randomly assigned to saline or surfactant therapy and treated within eight hours of birth. Significant improvements in oxygenation (increased arterial/alveolar PaO₂) and respiratory support (decreased mean airway pressure) were seen in the group receiving surfactant within four hours after treatment. These improvements were maintained in the surfactant-treated infants, who also had fewer pneumothoraces and fewer number of days in environments of fractional inspiratory oxygen greater than 0.4 mm Hg. No problems were associated with administration of surfactant, and no acute side effects were detected. We conclude that exogenous surfactant, administered early in the course of severe hyaline membrane disease, is an effective therapy that can diminish the amount of respiratory support required during the first 48 hours of life. Pediatric 1987;79:31-37; TA surfactant, hyaline membrane disease.

ABBREVIATIONS. a/A PaO₂, arterial/alveolar PaO₂; ANOVA, analysis of variance.

Advances in respiratory care have improved the outcome in newborn infants with hyaline membrane disease.1 Nevertheless, this disease remains an important cause of mortality and morbidity in the low birth weight infant,2 and, thus, therapies specifically designed to treat or prevent hyaline membrane disease would be of benefit in these infants. Exogenous surfactant may prove useful in accomplishing this goal.

Avery and Mead3 demonstrated a marked reduction in the surface-active material in saline extracts from the lungs of newborn infants with hyaline membrane disease. Early attempts to replace surfactant in infants with hyaline membrane disease were unsuccessful due to incomplete knowledge of surfactant composition and improper delivery methods.4 Most recently, Fujiwara et al5 have treated newborn infants with hyaline membrane disease using a well-characterized organic solvent extract of beef lung surfactant (surfactant TA). A dramatic decrease in oxygen requirement was demonstrated in these infants within three hours after treatment.5 Promising results have also been shown by Enhorning et al6 using a bovine surfactant and by Hallman et al7 using human surfactant isolated from term amniotic fluid.

We undertook the present study to critically assess the role of surfactant replacement in the treatment of hyaline membrane disease. We used a well-characterized surfactant preparation (surfactant TA) that has the potential of becoming widely available and is free of human pathogens.5,8 Our objective was to determine whether surfactant TA given within the first eight hours of life would reduce the need for ventilatory support and improve oxygenation in a well-defined group of infants with severe hyaline membrane disease. In addition, the study allowed for an initial assessment of acute problems associated with this therapy.
METHODS

Patient Population

Patients were enrolled from a total of 2,383 newborns admitted to the neonatal intensive care units of the Brigham and Women’s Hospital, Boston, the Children’s Hospital, Boston, and the Medical Center Hospital of Vermont, Burlington, between November 1983 and March 1985. Appropriate for gestational age infants with birth weights between 1,000 and 1,500 g having clinical and roentgenographic findings consistent with hyaline membrane disease were enrolled and treated by eight hours of life. We limited our study to infants who at the time of enrollment required mechanical ventilation and a fractional inspiratory oxygen concentration (FiO₂) > 0.4 mm Hg to maintain an arterial PaO₂ > 50 mm Hg (severe hyaline membrane disease). From a total of 258 infants in the weight group appropriate for the study, 50 infants met study criteria, and 41 patients were enrolled. Three patients were not enrolled because the investigators were not contacted. For four patients, the parents refused consent, and for two infants, investigators deemed the parents were not competent to give consent.

The study was conducted concurrently in three different neonatal intensive care units. In one nursery, patients were enrolled from a population of outborn, transported infants (Children’s Hospital, Boston), and in the other two nurseries, patients were enrolled from a population of inborn infants. Attempts were made to standardize care at the nurseries involved despite the different population bases served. Similar numbers of patients were enrolled from each of the three nurseries involved. Previously published diagnostic and therapeutic regimens were used for the diagnosis and management of patent ductus arteriosus and other associated clinical conditions. Intracranial hemorrhages were diagnosed with real-time sector scanning and graded according to published criteria. Cranial ultrasound examination was performed on all patients within the first days of life. The study was reviewed and approved by the appropriate human studies and investigation committees for each hospital.

Surfactant Administration

The surfactant used in this study has been previously characterized by Fujiwara et al. Tokyo Akita (TA) surfactant is an organic solvent extract of minced beef lung that has been supplemented to predetermined standard concentrations of dipalmitoyl phosphatidylcholine, tripalmitin, and palmitic acid. It contains one of the previously characterized unique surfactant-associated proteins. In vivo and in vitro testing of multiple batches have shown it to be an effective surfactant. A single batch (TA 37) was supplied to us by Tokyo Tanabe Company as a sterile white lyophilized powder (100-mg vial) stored under nitrogen at −20°C. The surfactant was resuspended in 3.3 mL of sterile saline, sonicated to a homogeneous dispersion, and passed through a 25-gauge needle immediately prior to administration. The study was not blinded because no safe placebo with physical characteristics similar to the surfactant preparation could be designed. Approval for use in human trials was obtained from the Federal Drug Administration (IND #22518).

Baseline values for arterial/alveolar Po₂ (a/Alveolar Po₂) and mean airway pressure were obtained 30 minutes and five minutes prior to therapy. Surfactant was instilled directly via a 3.5 F catheter that was passed to the tip of the endotracheal tube. In four divided doses, 3.3 mL/kg was given over two minutes. To promote uniform distribution, the infant was turned after each quarter dose (thorax up and then down positioned first, to the right, then the left) and manually ventilated with 100% oxygen at pressures equal to previous ventilator settings. Control infants were treated with sterile saline in a volume (1.5 mL) routinely used for endotracheal suctioning in our nurseries. During the administration of saline, infants were handled in a fashion identical with the surfactant-treated infants, including positioning and the use of 100% oxygen. Subsequent patient management was determined by staff neonatologists caring for the infants.

The mean airway pressure was measured in two nurseries (24 infants) using a Pneumogard device situated at the proximal airway (Novametrix Medical Systems), and in one nursery (17 infants) the mean airway pressure was calculated using a square waveform. A systematic difference of 2 to 3 cm H₂O was absorbed in our analysis as part of the internursery stratification.

Study Design

The study was designed to determine whether a single dose of surfactant TA administered early in the course of hyaline membrane disease would ameliorate the disease. Using data from a pilot study of four patients and previously published trials, we chose a/A Po₂ and mean airway pressure at 30 minutes, two hours, and 12 hours after administration as principal end points. The a/A Po₂ has been shown to accurately reflect gas exchange in acute pulmonary disease within a wide range of FiO₂ values and was calculated with an assumed respiratory quotient of 0.8. The pilot data suggested that we could expect a difference in
a/A P02 of 0.2 mm Hg between control and treated infants at two hours after treatment, and a difference in mean airway pressure of 2 cm H2O. Sample size calculations indicated that a sample size of 40 would allow us to detect these differences with 95% power and 5% probability of type I error (spurious significance). The design had adequate power (70% to 90%) to detect lesser differences expected at 30 minutes and 12 hours after treatment.

Patients were randomly allocated to treatment and control groups by the use of cards in sealed envelopes. Unknown to the clinical investigators, each series of six cards included three control and three treatment cards in random order. Twins were randomized consecutively. An advisory board consisting of members not engaged in the operation of the study (a senior neonatologist, a senior pediatrician, and a consulting statistician) periodically reviewed the data to monitor conduct of the study and to enable us to stop the study in the event of unforeseen side effects.

Data Analysis

Sex, race, birth weight, and gestational age were similarly distributed in control and treated infants. Nevertheless, we controlled for these variables in our analysis of the principal end points (a/A and mean airway pressure) to counteract any possible confounding with treatment. We adjusted the comparisons for pretreatment a/A and mean airway pressure even though these too were similarly distributed in control and treated infants. Because three different nurseries were involved in the trial, we also stratified the analysis to allow for intranursery variation. No treatment effect was judged significant unless it explained a significant amount of variability over and above what could be attributed to these concomitant variables. Our analysis also addressed interaction of treatment effects with sex, race, and nursery (eg, treatment being effective on one sex or nursery but not in another).

We used four similar statistical comparison procedures, selecting whichever was appropriate for the type of variable being compared. To compare continuous quantities with approximately gaussian variability (eg, birth weight), we used fixed-factor analysis of variance (ANOVA). As noted before, the principal factors were treatment, sex, race, and nursery. For continuous quantities with skewed distribution (eg, days in oxygen), we ranked the data and applied factorial ANOVA to the ranks.17 Analysis of principal end points was by the factorial ANOVA with four continuous covariates: birth weight, gestational age, and baseline measurements at 30 minutes and five minutes pretreatment. In the case of categorical outcomes (eg, mortality), we applied the GSK procedure, a discrete-variable analog of ANOVA.18

For the ranked and categorical variables (all secondary end points), the sample size of 41 was too small to permit stratification for sex and race without severe loss of statistical power. We did stratify for nursery in every case. Computations were carried out with the statistical package from SAS.19

RESULTS

Characteristics of the sample are shown in Table 1. There were no significant differences between the treated and control patients with respect to factors that might influence the course of hyaline membrane disease, including weight, gestational age, sex, and race. The degree of asphyxia as estimated by Apgar scores and cord blood gas values were similar in both groups (data not shown). In addition, the pretreatment ventilator management and respiratory status (as reflected by a/A P02 and mean airway pressure prior to treatment) were similar in both groups. All patients were treated between 5 and seven hours of age, and no significant differences in time until treatment were detected between groups (data not shown).

### Table 1. Comparison of Pretreatment Variables*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Treated (n = 18)</th>
<th>Control (n = 23)</th>
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</thead>
<tbody>
<tr>
<td>Birth wt (mean g ± SD)</td>
<td>1,238 ± 153</td>
<td>1,214 ± 151</td>
</tr>
<tr>
<td>Gestational age (mean wk ± SD)</td>
<td>29.0 ± 1.6</td>
<td>29.0 ± 1.5</td>
</tr>
<tr>
<td>Sex (No.)</td>
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<td></td>
</tr>
<tr>
<td>Female</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>Male</td>
<td>8</td>
<td>15</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
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<td>21</td>
</tr>
<tr>
<td>Black</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Prenatal steroids (No.)</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Maternal tocolytics (No.)</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>Cesarean section (No.)</td>
<td>12</td>
<td>14</td>
</tr>
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</table>

* No significant differences between treated and control groups, P > .10.
The effect of TA surfactant on gas exchange is illustrated in Fig 1. The a/A Po2 values were not significantly different at 30 minutes and five minutes before treatment in the two groups. All patients were followed with continuous transcutaneous oxygen monitoring, and no transient deterioration in oxygenation was seen after surfactant administration. A transient significant improvement in a/A Po2 was noted in the surfactant-treated group within 30 minutes ($P < .001$). By four hours after treatment, a rapid increase in the a/A Po2 was seen in the surfactant-treated group. This increase, which was significantly different from the saline-treated control infants, was maintained during the subsequent 48 hours after treatment (Fig 1). In contrast, the saline-treated infants did not demonstrate any change in a/A Po2 for the first 48 hours following treatment. These infants began a gradual improvement in a/A Po2 after 48 hours, and only by the third day did they begin to achieve values similar to those reached at four hours in the surfactant-treated group. The subsequent course of a/A Po2 values after three days remained similar in both groups.

The effect of surfactant TA on the second primary end point, mean airway pressure, is illustrated in Fig 2. There were not significant differences at 30 minutes and five minutes before treatment. By four hours after treatment, a rapid increase in the mean airway pressure was seen in the surfactant-treated group. This increase, which was significantly different from the saline-treated control infants, was maintained during the subsequent 48 hours after treatment. During this period, the mean airway pressure in the surfactant-treated group was significantly lower than in the saline-treated group ($P < .05$). The subsequent course of mean airway pressure after three days remained similar in both groups.

Fig 1. Arterial/alveolar $\text{PO}_2$ in surfactant-treated (▼) and control (○) infants. Bars indicate means ± SE after adjustment for any differences in distribution of sex, race, nursery, birth weight, gestational age, and pretreatment level between two groups. Statistically significant effects ($P < .005$) were seen between four and 48 hours after treatment.

Fig 2. Mean airway pressure in surfactant-treated (▼) and control (○) infants. Bars indicate means ± SE after adjustment for any differences in distribution of sex, race, nursery, birth weight, gestational age, and pretreatment level between two groups. Statistically significant effects ($P < .05$) were seen between 18 and 48 hours after treatment.
between the two groups. A significant reduction in the mean airway pressure in the surfactant-treated infants was noted by two hours after treatment. This improvement was rapid and was maintained during the next 72 hours. In contrast, the saline-treated infants had no decline in the mean airway pressure until the third day after treatment, when a gradual decline toward values seen in the surfactant-treated group was noted. These lower values were then maintained during the subsequent course of both groups of infants. Two infants who failed to respond to the initial TA surfactant dose were retreated 12 hours later, and again, no improvement was seen in mean airway pressure or a/A Po2.

Data on other outcomes related to respiratory support are shown in Table 2. Although the incidence of pulmonary interstitial emphysema was similar in both groups, significantly fewer pneumothoraces developed in infants treated with surfactant. A decrease in the need for respiratory support in this group was reflected by a significant decrease in both the number of days in FiO2 > 0.4 mm Hg and the total days in supplemental oxygen.

We also analyzed the requirements for respiratory support in the surviving infants by comparing the number of days from birth to extubation in the treated and control groups. A trend toward earlier extubation in surfactant-treated infants is illustrated in Fig 3. In the Burlington nursery, the difference was large. There was a median of three days to extubation in the treated infants and 17 days in the control infants. In the Boston nurseries, however, the difference was negligible, and in a combined analysis of nurseries, the effect of treatment on days to extubation was statistically insignificant (Table 2).

Data on serious neonatal complications are shown in Table 3. There were no significant differences in any of these outcomes between the saline-treated and the surfactant-treated infants. The incidence of these outcomes in both groups was similar to the overall incidence in our nurseries. Of note is the fact that the incidence of hemodynamically significant patent ductus arteriosus was similar in both groups, as were the numbers of infants requiring either medical management with indomethacin or surgical ligation. Mortality in both groups was due to either acute or chronic respiratory disease.

**DISCUSSION**

The findings from this study demonstrate that surfactant TA given early in the course of severe hyaline membrane disease leads to a prompt and sustained improvement in oxygenation and a decrease in the need for ventilatory support. The major effect, as seen in Figs 1 and 2, was to improve the a/A Po2 and decrease mean airway pressure during the first 72 hours after therapy. An improve-

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**TABLE 2.** Respiratory Complications and Duration of Respiratory Support

<table>
<thead>
<tr>
<th></th>
<th>Treated (n = 18)</th>
<th>Control (n = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of infants with:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary interstitial emphysema</td>
<td>4</td>
<td>11</td>
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<tr>
<td>Pneumothorax</td>
<td>3*</td>
<td>13</td>
</tr>
<tr>
<td>Median duration (survivors only) of</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days FiO2 ≥ 0.40</td>
<td>0.2*</td>
<td>3.0</td>
</tr>
<tr>
<td>Days in oxygen</td>
<td>7.0*</td>
<td>16.0</td>
</tr>
<tr>
<td>Days to extubation</td>
<td>4.0</td>
<td>11.0</td>
</tr>
</tbody>
</table>

*Significantly different from control group, P < .05.

**TABLE 3.** Mortality and Common Morbidities Associated With Prematurity and Hyaline Membrane Disease

<table>
<thead>
<tr>
<th></th>
<th>Treated (n = 18)</th>
<th>Control (n = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patent ductus arteriosus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Requiring indomethacin or surgery</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Requiring surgery</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Intraventricular hemorrhage</td>
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<td></td>
</tr>
<tr>
<td>Grade I-IV</td>
<td>9</td>
<td>11</td>
</tr>
<tr>
<td>Grade III-IV</td>
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<td>6</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Necrotizing enterocolitis</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Retinopathy of prematurity</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Bronchopulmonary dysplasia</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Mortality</td>
<td>3</td>
<td>6</td>
</tr>
</tbody>
</table>

* No significant differences between treated and control groups, P > .50.
ment in respiratory status during the first days of disease was also demonstrated by a decrease in the incidence of pneumothorax. This immediate respiratory improvement with surfactant treatment is important in light of recent data implicating both pneumothorax and early severe pulmonary disease with intracranial hemorrhage in this population.

In addition to these early beneficial effects, surfactant treatment may also result in a sustained improvement in respiratory function. This was best indicated by a significant reduction in the overall oxygen requirement of the surfactant-treated infants (Table 2). The analysis of the duration of ventilator support in the first month of life may also indicate a trend toward earlier respiratory improvement after surfactant treatment.

Recently, Enhornig et al studied a bovine surfactant administered prior to the first breath in low birth weight infants to prevent hyaline membrane disease. The risks of hyaline membrane disease and potential hazards of therapy in infants who may not need the therapy will be dependent upon the gestational maturity of infants studied. Our patients were larger and gestationally more mature than those of Enhornig et al and, thus, we chose a treatment rather than preventive strategy because we did not wish to expose infants at low risk to a new therapeutic regimen with unknown effects. Therefore, we defined a population of infants with severe hyaline membrane disease as the primary clinical problem to directly assess the effect of surfactant administration. The data in Table 1 indicate that the control and surfactant-treated infants were similar with respect to clinical variables that might influence the outcome of hyaline membrane disease. Furthermore, all patients were treated at similar times from birth, and the average values for \( \Delta A P_{O_2} \) and mean airway pressure before treatment were identical in both groups. No significant internursery variation of these values was detected. We concluded from these data that the improvement seen with surfactant therapy was not the result of differences in clinical characteristics, disease severity, or nursery management between the control and treated infants.

Results of prior studies of surfactant replacement in immature lambs suggest that different modes of ventilation may contribute to clinical improvement independent of alterations in alveolar pool size of surfactant. For this reason, we treated our control infants with saline instillation in a manner identical with that of surfactant-treated infants, including positioning during treatment. Although a small increase in \( \Delta A P_{O_2} \) values could be seen in the control group following treatment, this was not sustained, and by two hours after treatment, a significant difference was seen in the surfactant-treated group (Fig 1).

An increase in the incidence and severity of patent ductus arteriosus has been noted after experimental surfactant replacement. Recent experience with surfactant TA in nonhuman primates confirmed these findings, and an earlier onset of increased ductal blood flow in surfactant-treated animals was noted. In our study, the incidence and severity of hemodynamically significant patent ductus arteriosus was not increased in the surfactant-treated infants. Furthermore, the overall incidence was consistent with that seen previously in our nurseries. These data suggest that surfactant TA therapy in human infants does not increase the problems associated with a patent ductus arteriosus, despite previous experimental studies. This discrepancy may, in part, be due to distinct pathophysiologic differences between lung disease seen in experimental premature animal models and that which occurs in human infants.

Recently, Hallman and co-workers presented data suggesting a beneficial effect of amniotic fluid-derived human surfactant in the treatment of hyaline membrane disease. Their study reaches conclusions similar to ours despite some differences in treatment design. Important questions of availability, standardization, and safety of human-derived material remain. Safety is of particular concern with material concentrated from body fluids, given recent evidence concerning previously undetected infectious agents in material derived from other human sources. These issues are important if beneficial effects are to be translated into widespread clinical use. Surfactant TA may offer an advantage over human and other currently available exogenous surfactants in its potential for wide availability, quality control, and demonstrated efficacy. Nevertheless, long-term studies will be needed to ensure the safety of TA surfactant, especially in view of potential immunologic effects from bovine-derived material. These studies are currently in progress.

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