Safety and Potential Efficacy of an Aerosolized Surfactant in Human Sepsis-Induced Adult Respiratory Distress Syndrome

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Objective.—To evaluate the safety and potential efficacy of aerosolized surfactant in intubated patients with adult respiratory distress syndrome (ARDS).

Design.—A prospective, double-blind, placebo-controlled, randomized, parallel, multicenter pilot clinical trial.

Patients.—A total of 51 patients with sepsis-induced ARDS were entered into the study within 18 hours of developing sepsis or sepsis syndrome.

Intervention.—Patients were randomized into four treatment groups in a 2:1:2:1 ratio, as follows: 12 hours of surfactant per day, 12 hours of 0.6% saline per day, 24 hours of surfactant per day, and 24 hours of 0.6% saline per day. Surfactant or saline was aerosolized continuously for up to 5 days using an in-line nebulizer that aerosolized only during inspiration.

Main Outcome Measures.—Ventilatory data, arterial blood gases, and hemodynamic parameters were measured at baseline, every 4 or 8 hours during the 5 days of treatment, 24 hours after treatment, and 30 days after treatment, at which time mortality was also assessed. Safety was evaluated throughout the 30 days of the study.

Results.—Surfactant was administered safely in ventilated patients when given continuously throughout the 5 days using the nebulizer system. Although there were no differences in any physiological parameter between the treatment groups, there was a dose-dependent trend in reduction of mortality from 47% in the combined placebo group to 41% and 35% in the groups treated with 12 hours and 24 hours of surfactant per day, respectively.

Conclusions.—Aerosolized surfactant was well tolerated when administered on a continuous basis for up to 5 days; however, at the doses given, it did not result in significant improvements in patients with sepsis-induced ARDS.

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ALTHOUGH partially described by a variety of names for many years, adult respiratory distress syndrome (ARDS) first was described clearly in 1967.1 This syndrome has been associated with extraordinarily diverse predisposing and etiologic factors, including sepsis or sepsis syndrome, gastric aspiration, trauma, heroin and other drug overdose, multiple transfusions, fat emboli, chemical or smoke inhalation, burns, disseminated intravascular coagulation, viral pneumonia, pancreatitis, drug reactions, and near drowning.2 Following insult to the pulmonary capillary endothelium and/or the alveolar epithelium, high permeability pulmonary edema develops, the chest roentgenogram shows diffuse bilateral infiltrates, lung compliance falls, and extravascular lung water increases in the absence of left-sided heart failure.3 Hypoxemia persists despite high concentrations of supplemental oxygen due to intrapulmonary shunting.4 Although intrapulmonary shunting can be decreased with various ventilatory manipulations, including positive end-expiratory pressure, this often leads to a diminished cardiac output, which can imperil tissue oxygen delivery and utilization.5 Despite increasingly complex modes of mechanical ventilation, sophisticated respiratory and hemodynamic monitoring, and a continually expanding array of potent antibiotics, the overall mortality is estimated to have remained at 40% to 50% for the last two decades, and mortality increases precipitously with each organ that fails.6,7

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Even use of extracorporeal membrane oxygenation in prospective randomized trials has failed to reduce mortality.10

The similarity between ARDS and neonatal respiratory distress syndrome (NRDS) was noted in the first description of ARDS, and surfactant deficiency was postulated as a common mechanism of dysfunction.1 In both disorders, there is refractory hypoxemia, decreased lung compliance, bilateral infiltrates on chest roentgenogram, hyaline membrane formation, and surfactant dysfunction.11 It has already been demonstrated that surfactant replacement therapy reduces mortality and morbidity in NRDS.12,13

There is compelling evidence that surfactant replacement has a role in treatment of ARDS.

Numerous animal models of ARDS that examined a variety of injuries clearly demonstrate that surfactant dysfunction is present.14-16 Rapid injury, such as with antilung serum infusion, and more prolonged injury, such as oxygen toxicity, result in physiological changes similar to those seen in ARDS, and both are also associated with surfactant dysfunction.17,18 Surfactant replacement therapy improves physiology and survival in these animal models similar to that seen in NRDS.15,19

Surfactant dysfunction is also present in humans with ARDS. Patients with trauma-induced ARDS have surfactant dysfunction in proportion to the severity of their disease.20 Surfactant dysfunction is also present in patients at risk of developing ARDS, and increasing dysfunction is seen in patients who proceed to develop ARDS.21

Surfactant therapy for ARDS in humans has been limited to a few case reports where surfactant was used in nonrandomized, open-label fashion.22 These anecdotal reports describe remarkable benefits in some patients. These results are encouraging and in general support the role of surfactant dysfunction as a component of ARDS.

The purpose of this pilot study was to evaluate aerosolized surfactant replacement therapy in a multicenter, randomized, double-blind, placebo-controlled dose comparison in patients with sepsis-induced ARDS. The objectives were to evaluate the safety and potential efficacy of continuously aerosolized synthetic surfactant in intubated patients with ARDS in preparation for a larger, definitive trial.

METHODS

Design

This study was a double-blind, placebo-controlled, multicenter, randomized, parallel-design, pilot-dose comparator of the effect of aerosolized surfactant or saline on sepsis-induced ARDS. Patients were randomized in a 2:1:2:1 ratio, respectively, into the following four treatment groups: 12 hours of aerosolized surfactant per day (Surf-12), 12 hours of aerosolized 0.6% saline per day (placebo), 24 hours of aerosolized surfactant per day (Surf-24), and 24 hours of aerosolized 0.6% saline per day (placebo). Randomization was performed by a central office at the time of entry, using an interactive computer program that maintained comparable numbers entered into all groups at each site and across all sites. The study consisted of a screening phase, a 5-day treatment phase, a 24-hour posttreatment phase, and a 30-day follow-up. The study was carried out in 20 tertiary care medical centers throughout the United States and was approved by the institutional review board of each institution.

Patients

Patients who met the following criteria were eligible for the study: (1) males or females age 5 years or older; (2) intubation and mechanical ventilation; (3) presence of a pulmonary balloon-flotation catheter; (4) clinical evidence of ARDS as defined by both a hypoxemia ratio (partial pressure of oxygen, arterial/fraction of inspired oxygen [PaO2/FIO2]) from 50 through 299 and diffuse bilateral infiltrates on chest roentgenogram; and (5) sepsis as documented by a positive blood culture, or sepsis syndrome as recently defined23 as high clinical suspicion of infection, core temperature greater than 38.5°C (not required if receiving antipyretics) or less than 35.6°C, heart rate greater than 90 beats per minute (not required if the patient was receiving beta blockers or calcium channel blockers) and respirations greater than 20 breaths per minute, and evidence of inadequate perfusion by one of the following: hypoxemia, PaO2 less than 75 mm Hg with an FIO2 of 21% not due to chronic lung disease, elevated serum lactate, change in mental status, or decrease in urine output to less than 30 mL/h for 2 hours despite fluid replacement. Patients were required to enter the study within 18 hours of the identification of sepsis or sepsis syndrome.

Patients were excluded from the study for any of the following reasons: (1) electrocardiographic evidence of coronary artery ischemia or infarction, or a pulmonary capillary wedge pressure greater than 22 mm Hg; (2) bacterial pneumonia, Pneumocystis carinii infection, or other compromising pulmonary infections; (3) renal failure defined as serum creatinine level of 220 µmol/L (2.5 mg/dL) or more or sustained oliguria for greater than 2 hours (urine output <30 mL/h for adults and <0.5 mL per kilogram of body weight per hour for children <18 years old); (4) hepatic failure defined as a bilirubin level greater than 86 µmol/L (5.0 mg/dL), or alanine aminotransferase or aspartate aminotransferase greater than five times the upper limit of normal; (5) patients known to have acquired immunodeficiency syndrome; (6) pregnancy; (7) chronic medication for chronic obstructive lung disease, asthma, or emphysema; and (8) any physiological or psychological condition other than ARDS that contraindicated the administration of surfactant.

General Assessments

The following general assessments to evaluate safety and potential efficacy were obtained on entrance into the study: a thorough medical history, thorough physical examination, electrocardiogram, hematologic evaluation (hemoglobin, hematocrit, white blood cell count and differential, platelet count, and red blood cell count and composition), blood chemistries (albumin, alkaline phosphatase, calcium, carbon dioxide, chloride, cholesterol, creatinine, glucose, lactate, dehydrogenase, phosphorus, potassium, sodium, total protein, triglyceride, γ-glutamyltransaminase, alanine aminotransferase, aspartate aminotransferase, total bilirubin, urea, and uric acid), urinalysis (pH, glucose, ketones, protein, bilirubin, and blood), APACHE II (Acute Physiology and Chronic Health Evaluation II) score, a chest roentgenogram, and cultures of blood and other appropriate sites. These assessments were repeated within the 24-hour period after aerosolization had been discontinued and 30 days after the study began. The number of days of hospitalization were evaluated at hospital discharge or at 30 days. Chest roentgenograms were evaluated by a single radiologist blinded to the treatment group. Mortality was assessed 30 days after treatment began, and the cause of death was documented.

The patient was continuously monitored for any adverse experiences, which were rated according to intensity, seriousness, and causality to study drug. An adverse experience was defined as any untoward outcome and was rated as attributable to the study drug or its delivery or would not be expected in patients with ARDS related to sepsis. The investigator recorded each adverse event, including an estimate of duration, intensity, seriousness, causality, and interventions undertaken.

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Respiratory and Hemodynamic Assessments

Respiratory and hemodynamic assessments were also obtained to evaluate safety and potential efficacy. At baseline, every 4 hours, and when the nebulizer was turned off and on throughout the 5-day treatment period, the following ventilatory data were obtained: intubation status, FiO₂, ventilator mode, positive end-expiratory pressure, peak inspiratory pressure, tidal volume, plateau pressure, and respiratory rate. From these data, the dynamic and static respiratory system compliance was calculated. The number of days the patient was on mechanical ventilation during the 30 days of the study was also recorded.

At baseline and every 4 hours during the treatment period, the following were obtained: hypoxemia ratio (PaO₂/FiO₂), temperature, hemodynamic data (heart rate, pulmonary capillary wedge pressure, mean right atrial pressure, and the systolic, diastolic, and mean arterial and pulmonary artery blood pressures), arterial blood gas, and mixed venous blood gas. From these data, the alveolar-arterial oxygen gradient (P(A-a)O₂), arterial/alveolar oxygen ratio (PaO₂/P(A-a)O₂), shunt fraction, arteriovenous oxygen difference, and lung injury score were calculated. Thermodilution cardiac output was determined every 8 hours during treatment and used in determining the systemic oxygen transport.

All hemodynamic and respiratory parameters were repeated every 4 hours for 24 hours after discontinuation of treatment. These parameters were repeated at the 30-day follow-up if the patient was still being ventilated and a pulmonary balloon flotation catheter was in place. If not ventilated, spirometry, lung volumes, and single breath carbon monoxide diffusing capacity were obtained.

Surfactant Administration

The surfactant administered in this study (Exosurf, Burroughs Wellcome Co, Research Triangle Park, NC) is a synthetic surfactant developed by Clements.25 It is a mixture of dipalmitoyl phosphatidylcholine (DPPC), cetyl alcohol (hexadecanol), tyloxapol, and sodium chloride, with a ratio of 13.5:1:5:1:0.5:8, respectively. The surfactant was formulated as a sterile lyophilized powder and contains 13.5 mg of DPPC per milliliter after reconstitution with sterile water.

After randomization, the pharmacist placed 175 mL of surfactant or 0.5% saline in an opaque nebulizer (TriNeb, Vortran Medical Technology Inc, Sacramento, Calif); a new canister was used every 4 hours and was weighed before and after use. The nebulizer produces particles with a mass median diameter of approximately 2.2 μm. Surfactant or saline was aerosolized continuously for up to 5 days using an in-line nebulizer (VISAN, Vortran Medical Technology Inc) that aerosolized only during inspiration.26 The air flow through the nebulizer was set to deliver approximately one half of the tidal volume.

Statistical Methods

The objectives of this study were to evaluate the safety and potential efficacy of continuously aerosolized synthetic surfactant in preparation for a larger, definitive trial. Thus, no sample size or power calculations were done a priori.

There were no differences in results between the two placebo groups (12- and 24-hour administration of 0.6% saline per day). Thus, the placebo groups were combined for all subsequent analyses.

Presenting medical histories and physical examinations were tabulated and compared for intergroup differences. Changes in physiological parameters during the treatment period were compared using an average area under the curve (AAUC). The AAUC was derived by plotting the physiological data collected repeatedly every 4 hours during the treatment period, baseline (hour 0) through hour 120, with the parameter on the y-axis and time on the x-axis. Area under the curve (AUC) was then calculated for each patient’s data. Since the AUC values would be large and not meaningful to the clinician, the individual patient AUCs were then divided by 120 hours of treatment to yield a more familiar and meaningful value (AAUC).

For patients not receiving the full 120 hours of treatment, the last recorded value was carried forward to lessen the impact on the AUC for patients who did not complete the entire 5 days of treatment and to better represent their ultimate status (success or failure) throughout the study. Change from baseline AAUC was calculated by subtracting each patient’s baseline values from their AAUC. Nonparametric confidence intervals (CIs) based on Wilcoxon’s Rank-Sum Test27 were constructed for the comparison of the change from baseline AAUC values between the combined placebo groups and the surfactant-treated groups. Nonparametric intervals based on Wilcoxon’s Sign-Rank Test were constructed on the change from baseline AAUC data to detect change over time.

Mortality was assessed using Fisher’s Exact Test for survival at 30 days. This analysis was selected because the hypothesis of choice is a change in survival rate rather than an increase in survival time. Roentgenograms were categorized according to the degree of consolidation, atelectasis, hyperinflation, and effusion using a numeric score from 0 (none) to 3 (severe) in all five lobes. In addition, a general overall score of improvement or worsening was compared between groups. The number of days on mechanical ventilation, in the intensive care unit, receiving supplemental oxygen, and in the hospital were displayed using Kaplan-Meier plots.

In addition to evaluation of all physiological parameters for worsening, safety was also evaluated by the incidence of adverse experiences, expected complications of ARDS, and new physiological examination abnormalities or new diseases identified during treatment or the follow-up period, using 95% CIs. Changes from baseline for hematology and clinical chemistry parameters were compared using nonparametric 95% CIs and on difference between treatment groups and the placebo group.

RESULTS

Patient Demographics, Accountability, and Surfactant Dosage

Fifty-one patients were entered into the study: 17 in the combined placebo group, and 17 in each surfactant-treated group. Other than a preponderance of females in the placebo group and males in the Surf-24 group, there were no notable differences between groups in age, smoking history, body temperature, mean systemic arterial blood pressure, or APACHE II score (Table 1). At screening, blood cultures with gram-negative organisms were found in two patients in the placebo group, none in the Surf-12 group, and one in the Surf-24 group; gram-positive organisms were found in three patients in the Surf-24 group. The major pulmonary physiological parameters were not statistically different between all groups at baseline (Table 2).

There were 10, 12, and 12 patients in the placebo, Surf-12, and Surf-24 groups, respectively, who completed a full 5 days of treatment. Reasons for not completing the full course of therapy included mechanical ventilation discontinued in six patients (two in each group), death in three patients (one in each treatment group), adverse experiences unrelated to the study in three patients (one in the placebo group and two in the Surf-12 group), attending physician clinical decision to change to a ventilation mode or ventilator incompatible with the nebulizer in two patients (one each in the
Table 1.—Demographic and Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Treatment Group*</th>
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<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Surf-12</td>
<td>Surf-24</td>
<td></td>
</tr>
<tr>
<td>No. of Patients</td>
<td>17</td>
<td>17</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Female</td>
<td>12</td>
<td>10</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>5</td>
<td>7</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Mean (±SD) age, y</td>
<td>51 (±19)</td>
<td>51 (±20)</td>
<td>53 (±17)</td>
<td></td>
</tr>
<tr>
<td>Current smokers, %</td>
<td>41</td>
<td>53</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>Mean (±SD) body temperature, °C</td>
<td>38.0 (±0.7)</td>
<td>38.4 (±0.8)</td>
<td>38.2 (±1.0)</td>
<td></td>
</tr>
<tr>
<td>Mean (±SD) systemic arterial blood pressure, mm Hg</td>
<td>80.0 (±21)</td>
<td>79.7 (±15.2)</td>
<td>75.0 (±12.0)</td>
<td></td>
</tr>
<tr>
<td>Mean APACHE II† score</td>
<td>14.2 (±6.4)</td>
<td>16.5 (±6.7)</td>
<td>15.7 (±6.6)</td>
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</tbody>
</table>

*The placebo group received 0.6% saline for 12 or 24 hours per day; Surf-12 and Surf-24 indicate patients who received surfactant for 12 and 24 hours per day, respectively.
†APACHE II indicates Acute Physiology and Chronic Health Evaluation II.

Table 2.—Mean Values and Average Area Under the Curve for Change From Baseline for Major Physiologic Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Treatment Group</th>
<th>Baseline, Mean (SE)</th>
<th>AAUC Change From Baseline, Mean (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Surf-12</td>
<td>Surf-24</td>
</tr>
<tr>
<td>Shunt fraction, %</td>
<td>32.6 (3.8)</td>
<td>31.5 (3.4)</td>
<td>31.5 (3.4)</td>
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<tr>
<td>FIO₂, %</td>
<td>66.5 (5.6)</td>
<td>68.2 (3.5)</td>
<td>68.8 (4.9)</td>
</tr>
<tr>
<td>Paco₂/Fio₂ ratio</td>
<td>146.5 (20.4)</td>
<td>124.2 (11.8)</td>
<td>161.5 (16.2)</td>
</tr>
<tr>
<td>P (A–a)O₂, mm Hg</td>
<td>352.3 (43.6)</td>
<td>357.2 (25.0)</td>
<td>335.1 (33.2)</td>
</tr>
<tr>
<td>P(a/A)O₂, mm Hg</td>
<td>352.3 (43.6)</td>
<td>357.2 (25.0)</td>
<td>335.1 (33.2)</td>
</tr>
<tr>
<td>PEEP, mm Hg</td>
<td>4.0 (1.1)</td>
<td>4.0 (1.2)</td>
<td>4.0 (1.2)</td>
</tr>
<tr>
<td>PIP, mm Hg</td>
<td>42.4 (3.1)</td>
<td>47.0 (3.2)</td>
<td>42.3 (2.5)</td>
</tr>
<tr>
<td>Compliance, mL/cm H₂O</td>
<td>32.0 (2.6)</td>
<td>30.8 (3.1)</td>
<td>37.1 (2.7)</td>
</tr>
<tr>
<td>Static</td>
<td>Placebo</td>
<td>Surf-12</td>
<td>Surf-24</td>
</tr>
<tr>
<td>Dynamic</td>
<td>Placebo</td>
<td>Surf-12</td>
<td>Surf-24</td>
</tr>
</tbody>
</table>

*AAUC indicates average area under the curve; FIO₂, fraction of inspired oxygen; Paco₂, partial pressure of oxygen, arterial; P(A–a)O₂, arterial/alveolar oxygen difference in partial pressure of oxygen; P(a/A)O₂, arterial/alveolar oxygen ratio; PEEP, positive end-expiratory pressure; and PIP, peak inspiratory pressure.
†Statistically significant change from baseline (P<.05).

Survival of the patient groups treated with 0.6% saline for 12 or 24 hours per day was extremely well tolerated. However, pneumothorax occurred in one patient in the Surf-12 group, presumably due to partial occlusion of the ventilator exhalation bacteria filter with aerosol particles. Another patient in the Surf-24 group had a known cause that resolved spontaneously while continuing surfactant therapy.

Comparisons within the placebo group given 0.6% saline for 12 hours per day showed no changes in any parameters while on or off therapy. In addition, there were no differences between patients in the placebo group treated 12 hours per day compared with those given placebo 24 hours per day. Thus, nebulization of 0.6% saline appeared to have no adverse effects.

There were no consistent deteriorations in blood chemistry and hematologic values during treatment within or among the placebo, Surf-12, or Surf-24 groups. There were also no differences between groups in use of concomitant drug therapy, including acetaminophen, antibiotics, antifungals, antihypertensives, antivirals, aspirin, bronchodilators, glucocorticoids, mineralocorticoids, ibuprofen, indomethacin, paralytic agents, sedatives, or vasopressor agents. Results of most electrocardiograms were abnormal at baseline, and there were no consistent changes during treatment within or among treatment groups. Similarly, there were no consistent changes in physical findings or medical histories during treatment among treatment groups.

Efficacy

Although the major objective was to assess safety, potential efficacy was also evaluated. There was a rank order decrease in mortality at 30 days with a mortality of 47%, 41%, and 56% in the placebo, Surf-12, and Surf-24 groups, respectively (Figure). At 14 days, mortality was 35%, 24%, and 24% in the placebo, Surf-12, and Surf-24 groups, re-
spective. At 10 days, the mortality was 29%, 18%, and 6% in the placebo, Surfl-12, and Surf-24 groups, respectively. These changes were not statistically significant. With the number of patients in each treatment group, there was 10% power (β=.9, α=.05) to detect a difference in mortality between 47% in the placebo group and 37% in each treatment group. The causes of death were not notably different between groups, with multisystem organ failure and overwhelming sepsis with cardiovascular collapse as the most common causes of death. Respiratory failure was listed as the cause of death in one patient from the placebo group and two patients from the Surf-24 group.

The mean baseline and mean AAUC change from baseline for the major physiological values are shown in Table 2. Comparing within each treatment group, there were statistically significant improvements from baseline in Pa02/FIO2, P(A-a)O2, and P(A-a)02 in the placebo group, shunt fraction, Pa02/FIO2, FIO2, and P(A-a)02 in the Surf-12 group, and P(A-a)O2 and FIO2 in the Surf-24 group. In comparison between treatment groups, there were no significant differences seen. All groups had similar changes in positive end-expiratory pressure and compliance, and although not shown in the table, there were no differences in other pulmonary and hemodynamic assessments, such as peak inspiratory pressure, arteriovenous oxygen difference, pulmonary capillary wedge pressure, and cardiac output.

The number of days in the hospital was not significantly different between the treatment groups. Similarly, there were no significant differences in improvement of chest roentgenograms between the treatment groups.

COMMENT

This first placebo-controlled clinical trial of the effects of surfactant replacement therapy in patients with ARDS indicates that aerosolized surfactant is safe when given to intubated, mechanically ventilated patients. The safety of aerosolized surfactant therapy given with each breath continuously for up to 5 days is evident by the lack of any detrimental laboratory changes and the few adverse events recorded during therapy. There was no pneumothorax caused by increased airway pressures due to partial occlusion of the ventilator exhalation bacteria filter. Caution must be taken when aerosolizing large amounts of drug into a ventilatory circuit; use of specially designed equipment is required.34

Although improvement in the surfactant-treated groups was not dramatic, the trends in mortality in this pilot study are encouraging. The trends appear to be greater when evaluated earlier after treatment. The difference between the 10-day and 30-day mortality may indicate the importance of late, nonrespiratory causes of death, although there were no differences in causes of mortality identified in the study.

The mechanism of action for a potential reduction in mortality includes the surface tension–lowering capability and the antiedemic effects of surfactant. However, other mechanisms of action may also play a role. For example, surfactant causes a dose-dependent inhibition of interleukin-1, interleukin-6, and tumor necrosis factor release from stimulated human macrophages in vitro.35 A marked concentration-dependent suppression of phytohemagglutinin-induced immunoglobulin has also been demonstrated.36 These and as yet unreported mediations of the ongoing systemic inflammatory reaction that underlies ARDS or multiple organ dysfunction syndrome may account for an important component of the potential therapeutic efficacy of surfactant replacement.

The lack of effect on physiology in this pilot trial could be attributed to the lack of a role of surfactant in ARDS, use of an inappropriate surfactant, use of aerosol delivery, or an inappropriate dose achieved. The rationale for surfactant replacement in ARDS is supported by many human and animal studies.11,15-30 The surfactant used has proven to be safe and effective in extensive studies in NRDS.22,25 Aerosol delivery of surfactant was chosen because it is less invasive than delivering a large intra-tracheal bolus. After aerosolization, surfactant remains functional, and in animal models, aerosolized surfactant has been more effective than a single bolus delivery in an adult lung model.31 The nebulizer used in this study produces a relatively homogenous particle size distribution with a mass median diameter of approximately 2.2 μm.32 This particle size should give adequate deposition to the alveolar regions of the lung.

Most studies in animal models of ARDS have used a bolus of 100 mg of DPPC per kilogram as an effective dose; however, aerosolization may be more efficient than bolus instillation and the beneficial dose required for aerosol application has not been established. The amount aerosolized in this study was approximately 44 mg of DPPC per kilogram per day. The actual amount deposited in the lung would be expected to be similar to other aerosolized drugs in intubated patients, or 2% to 5% of that aerosolized.33 Thus, a likely reason for lack of effectiveness is the small dose delivered to the alveolar space. Inactivation by serum proteins can be overcome by increasing the dose of surfactant.34 Therefore, more profound effects on mortality and pulmonary physiology may be seen with higher doses of surfactant.

Patients with sepsis-induced ARDS were used in this study because sepsis is one of the most common causes of ARDS, results in a high mortality rate, and decreases the variability that would occur by including multiple causes of ARDS. Although patients with sepsis may not be homogeneous, the variability in response would be increased further using patients with other causes of ARDS. The definition used meets recent American College of Chest Physicians-Society of Critical Care Medicine Consensus Conference guidelines for the definitions of sepsis and septic shock in septic shock in sepsis.37 The Pao2/FIO2 ratio and the pulmonary capillary wedge pressure criteria used were purposefully chosen to be more inclusive than those used in previous studies, since surfactant therapy should be useful in milder forms of ARDS or ARDS complicated with mild elevated pulmonary capillary wedge pressure.

Previous studies have not been randomized or placebo-controlled. Randomization to a concurrent control group was essential for comparisons in this study. The control group received 0.6% saline through the same nebulizer system to control for potential effects from the nebulizer, to help maintain the blinding of treatment group assignment, and to have a similar salt content as the surfactant suspension. Although aerosolization of saline may have some effects on pulmonary function, the 30-day mortality of 47% in the placebo group is similar to other studies of sepsis-induced ARDS or sepsis,38 and there were no effects of aerosolization of 0.6% saline seen in the placebo groups when analyzed separately.39

Although surfactant therapy in patients with sepsis-induced ARDS did not result in any statistically significant differences in this pilot study, it is likely that the dose achieved was not large enough to counteract the inhibitors present in the lungs in patients with ARDS. A controlled trial with more patients using larger doses of surfactant may be more effective.

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