Pediatric Calfactant in Acute Respiratory Distress Syndrome Trial*

Douglas F. Willson, MD[1]; Neal J. Thomas, MD, MSc[2]; Robert Tamburro, MD[2]; Edward Truemper, MD[3]; Jonathon Truwit, MD, MBA[4]; Mark Conaway, PhD[5]; Christine Traul, MD[1,6]; Edmund E. Egan, MD[7,8]; for the Pediatric Acute Lung and Sepsis Investigators Network

Rationale: Our previous studies in children with acute lung injury/acute respiratory distress syndrome demonstrated improved outcomes with exogenous surfactant (calfactant) administration. Sample sizes in those studies were small, however, and the subject populations heterogeneous, thus making recommendations tenuous.

Objective: To investigate the efficacy of surfactant administration in a larger, more homogenous population of children with lung injury/acute respiratory distress syndrome due to direct lung injury.

Design and Setting: Masked, randomized, placebo-controlled trial in 24 children's hospitals in six different countries.

Patients and Methods: Children 37 weeks postconception to 18 years old with lung injury/acute respiratory distress syndrome due to direct lung injury were randomized to receive up to three doses of 30 mg/cm height of surfactant (calfactant) versus placebo (air) within 48 hours of intubation and initiation of mechanical ventilation. The primary outcome was mortality at 90 days. Ventilator-free days, changes in oxygenation, and adverse events were also assessed.

Results: The study was stopped at the sponsor's request after the second interim analysis for presumed futility. A total of 110 subjects were enrolled, with consent withdrawn from one whose data are unavailable. There were no significant differences between groups except in hospital-free days (10.4 ± 7.8 placebo vs 6.4 ± 7.8 surfactant; $p = 0.01$). Overall 90-day mortality was 11% (seven surfactant, five placebo). No immediate improvement in oxygenation was associated with surfactant administration.

Conclusions: Surfactant did not improve outcomes relative to placebo in this trial of children with direct lung injury/acute respiratory distress syndrome. Differences in concentration of the surfactant, failure to recruit the lung during surfactant administration, or using two rather than four position changes during administration are possible explanations for the difference from previous studies. Exogenous surfactant cannot be recommended at this time for children with direct lung injury/acute respiratory distress syndrome. (*Pediatr Crit Care Med* 2013; 14:657–665)

Key Words: acute lung injury; acute respiratory distress syndrome; calfactant; direct lung injury; hypoxemia index; oxygen saturation index; recruitment maneuver; respiratory failure; surfactant

***See also p. 716.**

[1]Department of Pediatrics, University of Virginia Health Sciences System, Charlottesville, VA.

[2]Department of Pediatrics, Penn State Hershey M.S. Hershey Medical Center, Hershey, PA.

[3]Department of Pediatrics, Children's Hospital & Medical Center, University of Nebraska, Omaha, NE.

[4]Department of Internal Medicine, University of Virginia Health Sciences System, Charlottesville, VA.

[5]Public Health Sciences, University of Virginia Health Sciences System, Charlottesville, VA.

[6]Department of Pediatrics, Children's Hospital Cleveland Clinic, Cleveland, OH.

[7]Pneuma Pharmaceuticals, Amherst, NY.

[8]Department of Pediatrics, State University of New York at Buffalo, Buffalo, NY.

Supported, in part, by Pneuma Pharmaceuticals, Amherst, NY.

The University of Virginia received compensation from Pneuma Pharmaceuticals to support, in part, the salaries of Drs. Willson, Truwit, Conaway, and Traul. Collaborating investigators were paid compensation for subjects successfully enrolled in the study and support for the work of their research assistants.

Dr. Willson received grant support from Pneuma Pharmaceuticals, support as a study coordinator, partial salary support, and capitation for enrolled subjects. Dr. Thomas received grant support from Pneuma Pharmaceuticals and served as a consultant for Discovery Laboratories. Dr. Tamburro received funding on a per patient basis (participating site in the trial) and received grant support from ONY, Inc. Dr. Truemper received grant support and support for travel from the University of Nebraska College of Medicine, provisions of the study drug (Cattactant - supplied to Children's Hospital and Medical Center for the duration of the trial), and lectured for the Nebraska Society of Respiratory Care. Dr. Truwit received support for travel from Pneuma Pharmaceuticals and grant support from Pneuma Pharmaceuticals, NIH, and ARDSNet. Dr. Conaway received support for participation in review activities from Pneuma Pharmaceuticals. Dr. Traul received grant support and support for travel from Pneuma Pharmaceuticals. Dr. Egan served as the unsalaried chairman and chief medical officer for Pneuma Pharmaceuticals, provided expert testimony for various insurance companies, and received funding from Pneuma Pharmaceuticals.

For information regarding this article, E-mail: dfw4m@virginia.edu

DOI: 10.1097/PCC.0b013e3182917b68

Surfactant plays an essential role in lung physiology, reducing overall surface tension at the lung air:fluid interface and varying surface tension during the respiratory cycle. As a consequence, the work of breathing is

minimized, the distribution of ventilation is equalized during inspiration, and surface tension–induced alveolar collapse at end expiration is prevented. The loss of lung aeration leading to respiratory failure in acute lung injury/acute respiratory distress syndrome (ALI/ARDS) is caused by both edema and atelectasis that may, in large part, be related to surfactant dysfunction. Multiple lines of evidence demonstrate that lung surfactant is dysfunctional in ALI/ARDS (1–8). Given the unequivocal success of exogenous surfactant administration in premature infants with respiratory failure due to lung surfactant deficiency (9), it has seemed plausible that surfactant replacement in ALI/ARDS might be therapeutic.

In three previous studies in children, we demonstrated that the administration of bovine natural surfactant, calfactant (Infasurf; ONY Pharmaceuticals, Amherst, NY), was associated with immediate improvement in oxygenation and, in the two studies with controls, better long-term outcomes, including decreased mortality (10–12). In our most recent study (12), the post hoc analysis demonstrated that improvement with surfactant administration was confined to the subjects with direct lung injury (lung injury that originates on the alveolar side of the alveolar-capillary membrane, such as pneumonia, aspiration, or near drowning). Consequently, the investigators elected to focus this investigation on that patient population. In view of the success of these earlier pediatric trials and the need to investigate possible efficacy in a larger but more homogeneous population, the investigators embarked on a multi-institutional trial of calfactant in both adults and children with direct ALI/ARDS. This article presents the results of the pediatric arm of the trial.

METHODS

Subjects were recruited from July 2008 to July 2010 from the ICUs of 24 children's hospitals in six countries (**Appendix 1**). The study, registered with clinicaltrials.gov (identifier NCT00682500), was performed in accordance with the Declaration of Helsinki (1996) and the rules of the International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use—Good Clinical Practice Consolidated Guideline. All patients or their legal representatives provided written informed consent and independent ethics committees or institutional review boards at each participating center approved the study protocol. An independent Data and Safety Monitoring Board (DSMB) monitored the study throughout. The study was stopped at the request of the sponsor, Pneuma Pharmaceuticals (Amherst, NY) after the planned second interim analysis at 400 subjects (combined adult and pediatric subjects) because of presumed futility.

Patient Population

Study coordinators at each site screened all ICU admissions. Children were eligible for the study if they were 37 weeks postconception to 18 years old, they met the American-European Consensus Conference definition of ALI/ARDS (13), they had direct lung injury (injury originating on the alveolar side of the alveolar capillary membrane), they were within 48 hours of the initiation of mechanical ventilation, they did not have significant other organ failure or chronic lung disease, and/or the scope and duration of their care were not limited by nonrespiratory disease. In the event of a question regarding eligibility, participating investigators were encouraged to contact the study primary investigator or study coordinator on call. All enrolled subjects were also subsequently reviewed by the study DSMB to ascertain suitability. If arterial blood gases were not obtained, oxygen saturation (Spo_2) could be substituted for Pao_2 in the entry criteria but an Spo_2/Fio_2 less than 250 (when $Spo_2 < 97\%$) was necessary to qualify. A log of intubated patients with ALI/ARDS was maintained at all institutions and the primary reason for not enrolling a potentially eligible patient recorded.

This study was a part of a combined adult and pediatric trial. Many of the participating hospitals admitted both adult and pediatric patients. A single research assistant commonly performed screening in those hospitals, but each hospital had separate adult and pediatric ICUs and appropriate subspecialists supervising the study in their respective areas.

Pediatric Study Arm

After initial demographic and qualifying data were entered on the study website, the participating site's pharmacy was automatically notified, and the pharmacist alone was provided the subject's assignment. The pharmacist then prepared the study drug, placing either air or calfactant in equal aliquots in two appropriately sized syringes, and the drug was delivered in an opaque container directly to the respiratory therapist and/or nurse for administration. Randomization was performed via the study website in blocks of four, and investigators were naïve to the randomization scheme. Subjects with an initial Pao_2/Fio_2 or Spo_2/Fio_2 less than 100, an oxygenation index (OI) > 30 ($OI = Fio_2 \cdot Paw \cdot 100 / Pao_2$, where Paw represents the mean airway pressure), or who were immune compromised were considered higher risk and were independently randomized in order to assure an even distribution of more severely ill subjects in both groups.

The study intervention consisted of direct instillation of up to three doses of calfactant 12 hours apart versus sham treatment with air placebo. The dose was 30 mg calfactant (phospholipid concentration of 60 mg/mL) per centimeter of height or 100 mg/kg for infants weighing less than 10 kg. The treatment was delivered in two equally divided aliquots instilled directly into the airway using a small catheter placed down the endotracheal tube. Subjects were sequentially turned right side down and then left side down during drug or placebo administration. The investigators elected to use two position changes rather than the four used in our previous studies in consideration of the greater difficulty incurred positioning the larger adults and concurrent with the desire to use the same protocol for the adult and pediatric arms of the trial. The Fio_2 was increased to 1.0 during instillation, and ventilator settings were otherwise unchanged unless there were difficulties during the intervention, in the event of which the caregiver was allowed to hand ventilate the subject with 100% oxygen at whatever pressure was necessary to achieve adequate oxygenation. In previous studies, subjects were "hand ventilated" during administration, but the investigators elected in this

study to perform the intervention while on the ventilator in the interest of minimizing variability in administration technique. Masking was accomplished by having the intervention performed by a nurse and/or respiratory therapist who was not otherwise involved in the care of the subject and who agreed to not divulge treatment assignment. Blood pressure, heart rate, and Spo_2 were continuously monitored and recorded every 5 minutes for 30 minutes after the intervention. Placebo subjects were treated identically with the exception that air was instilled rather than surfactant. To qualify for a subsequent dose, the subject had to demonstrate a 25% improvement in the Pao_2/Fio_2 ratio (or Spo_2/Fio_2) anytime in the 12 hours following the previous dose with no significant adverse effects attributable to the intervention. All subsequent interventions were delivered and masked using the same protocol.

Additional Protocols

As a precondition of trial participation, all investigators and their colleagues agreed in principle to follow guidelines modeled after the ARDS Network ventilator (14) and fluid guidelines (15) (**Figs. 1** and **2**). Investigators and study coordinators were instructed in both guidelines at the initial study visit and were given a supply of laminated cards with the fluid management and ventilator guidelines to distribute to colleagues caring for Calfactant in Acute Respiratory Distress Syndrome subjects in their institution. Since subjects were not required to have a central venous pressure (CVP) catheter for study entry, investigators were instructed to make judgments regarding fluid and/or diuretic administration based on daily fluid balance if CVP measurements were not available. No attempt was made by the principal investigators to direct the fluid management of specific patients during the trial, but daily fluid balances (total fluid in minus total fluid out over 24 hr without consideration of insensible losses) were collected over the first 7 days after subject enrollment as a means of ascertaining comparability of fluid management in placebo and surfactant subjects. Similarly, no attempt was made to regulate the ventilator management of individual subjects. Ventilator settings were collected during the first 7 days of the enrollment to ascertain any significant differences in ventilator management between the study populations. Since the investigators postulated that avoidance of lung overdistention was the most vital aspect of the protocol, this was assessed by tracking the incidence of a peak ventilator pressure greater than 30 cm H_2O and/or the use of a tidal volume greater than 8 cc/kg over the first 7 days after the study intervention.

All other aspects of care were left to the judgment of the attending physicians. Subjects discharged prior to 90 days were contacted by phone at 90 days to determine their health status.

Study Outcomes

The primary study outcome was all-cause mortality at 90 days after study entry. Secondary outcomes included ventilator-free days (VFDs) at 28 days, durations of ICU and hospital stay, and changes in oxygenation after the study intervention. Adverse events were followed throughout the period of hospitalization and assigned a relationship to the study intervention by the primary investigator at each site.

Data Collection

Ventilator settings, arterial blood gas results (if performed), and Spo_2 and end-tidal CO_2 ($Etco_2$) values were recorded at 1, 2, 4, 8, and 12 hours after each intervention and daily at approximately 08:00 hours for the first 7 days after study enrollment. Daily fluid balance was collected for the first 7 days as previously described. Demographics, as well as dates and times of intubation and extubation, and PICU and hospital admission and discharge were also collected. The duration of ventilation was calculated with successful extubation defined as 24 hours off mechanical ventilation and was computed as "VFDs at 28 days". Subjects dying before separation from mechanical ventilation were designated as having 0 VFDs. Subjects were followed daily until hospital discharge.

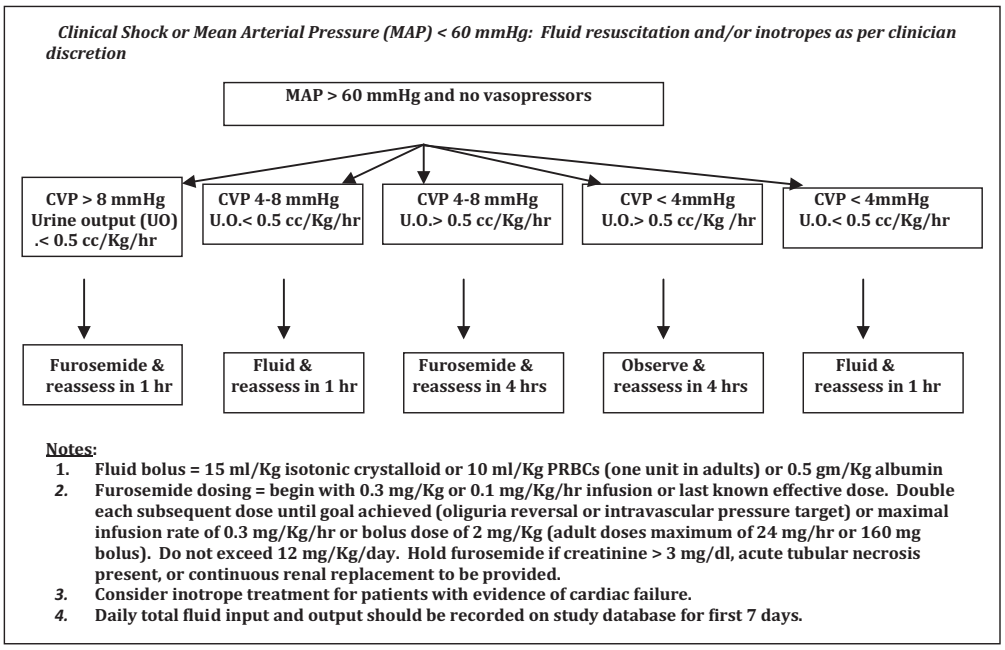
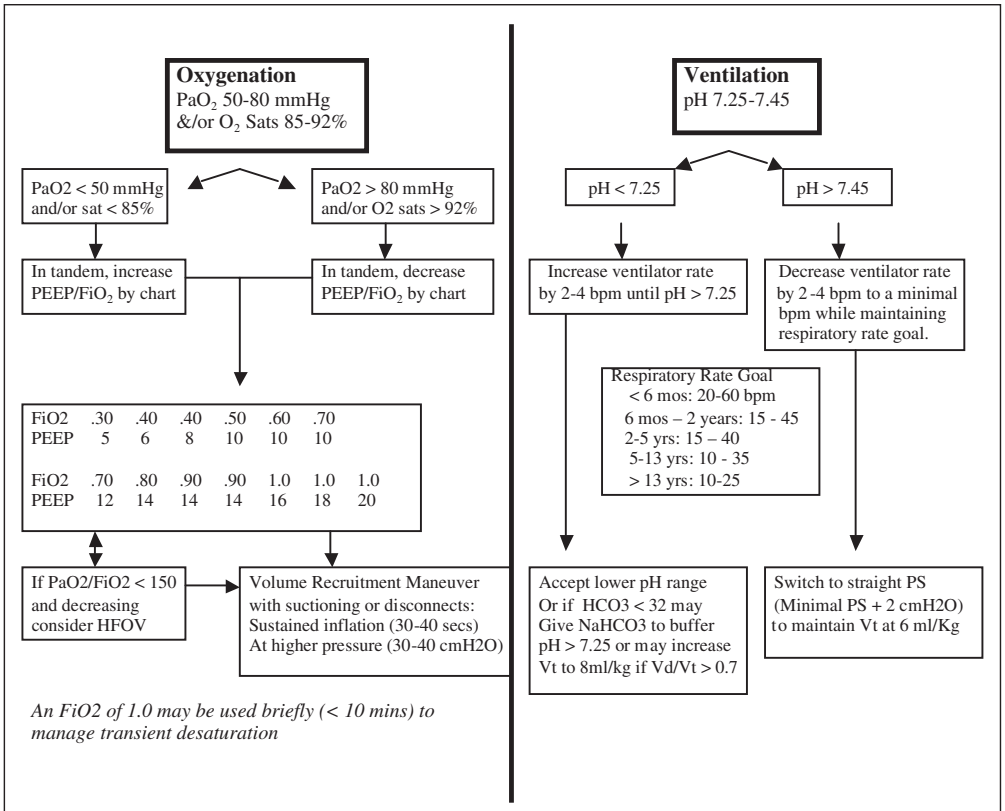


Figure 1. Simplified Fluid and Catheter Trial algorithm for fluid management. CVP = central venous pressure, PRBC = packed RBC.

Adult Study Arm

Eligible patients older than 18 years were entered into the adult study with identical inclusion/exclusion criteria and using the same protocol. Although most of the participating hospitals included both adult and pediatric patients, all pediatric subjects



Additional Notes

1. Weaning should be considered as soon as the patient is improving as evidenced by decreasing FiO2 requirements and decreasing ventilator pressures. Keys to weaning include daily evaluation to decrease pressure and/or FiO2 as well as assessment of sedation level.
2. In light of the fact that many patients are ready to extubate by the time they are evaluated for weaning, consider a daily "drug holiday" to allow sedation to lighten and a daily "spontaneous breathing trial" to evaluate suitability for weaning and/or extubation when and if appropriate.
3. Successful weaning and extubation requires 48 hours off positive pressure ventilatory support. CPAP alone does not constitute ventilatory support but cycled non-invasive positive pressure does (e.g., BIPAP)

Figure 2. Ventilator guidelines (adapted from Acute Respiratory Distress Syndrome Network guidelines) (14). PEEP = positive end-expiratory pressure, HFOV = high-frequency oscillatory ventilation, PS = pressure support, CPAP = continuous positive airway pressure, BIPAP = bilevel positive airway pressure.

were cared for in PICUs and all adult subjects in adult ICUs. These results will be reported in a separate article.

Statistical Methods

Sample size was calculated for the adult subject population. Assuming a 90-day mortality of 25% in the placebo group and 18% mortality in the calfactant group, enrolling 540 subjects in each group would give us an 80% power using an alpha (two sided) of 0.05. The pediatric arm was not powered for mortality because the required sample size was not considered attainable. However, the investigators assumed that approximately 300 pediatric subjects would be enrolled over the course of the projected 3 years of adult study. Using the results of our previous study with VFDs as our primary outcome, 300 subjects would yield 80% power for a 30% increase in VFDs; the attained sample size of 109 subjects would yield 80% power for a 50% increase in VFDs.

For comparing the placebo and surfactant groups, the chi-square test was used for categorical variables, and the Mann-Whitney nonparametric test was used for continuous variables. Linear regression was used to compare hospital days between groups, adjusting for age, gender, risk strata, immune status, fluid balance, and Pediatric Risk of Mortality (PRISM) score. Repeated measures models were used to compare the groups with respect to oxygenation measures taken 0, 1, 2, 4, 8, and 12 hours postintervention.

RESULTS

A total of 34,971 ventilated adult and pediatric subjects were screened, 2,949 of whom were identified as having direct ALI/ARDS. Of eligible subjects, 431 (15%) were entered into the trial, 110 children (< 18 years old) and 321 adults (**Fig. 3**). The reasons for study exclusion are displayed in Figure 3. One pediatric subject was randomized but not treated; consequently, these data are not available and are not included in this analysis. Fifty-three subjects received placebo and 56 were treated with calfactant surfactant. There were no significant differences in receiving a second or third intervention between groups; a second intervention was performed in 35% of surfactant subjects and 38% of placebo; only 5% of surfactant subjects received a third intervention compared with 13% in the placebo group.

Demographic data are found in **Table 1**. There were no significant differences between surfactant and placebo groups with respect to age, gender, diagnoses, or severity of illness as estimated by PRISM III, risk level, or initial oxygenation disturbance (Pao_2/Fio_2 or Spo_2/Fio_2). Pneumonia (viral, bacterial, and aspiration) was the most common etiology of ALI/ARDS. Twenty subjects were diagnosed with influenza; 14 had the H1N1 strain. A diagnosis of influenza was associated with 25% mortality (5/20) and H1N1 disease 21% (3/14) somewhat higher although not statistically different than the overall study mortality of 11% (12/109).

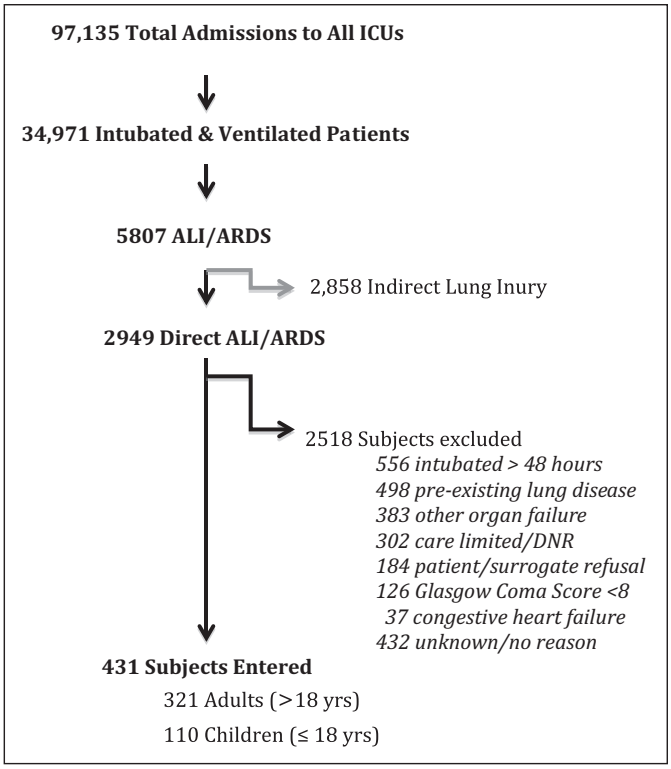


Figure 3. Flow chart for subject entry into Calfactant in Acute Respiratory Distress Syndrome (ARDS) trial. ALI = acute lung injury.

The administration of surfactant was not associated with improvement in oxygenation relative to placebo, irrespective of whether Pao_2/Fio_2 or Spo_2/Fio_2 ratios were analyzed (**Fig. 4**, *A* and *B*).

As with our previous studies, surfactant administration was associated with few adverse effects. There were 22 adverse events believed possibly or probably related to the study intervention: four episodes of transient hypoxia (three surfactants, one placebo); bradycardia in two surfactant subjects; and one episode of leukopenia in a surfactant subject. The only serious adverse events were one pneumothorax and one pneumomediastinum, both in surfactant subjects. The pneumothorax required chest tube placement, but no intervention was required for the pneumomediastinum. All subjects with adverse events believed possibly or probably related to the study intervention recovered without sequelae.

Study outcomes are found in **Table 2**. The primary study outcome was survival at 90 days, which was not different between the two groups. Overall mortality was 11%. Seven surfactant subjects died (12%) and five placebo subjects (9%), two after hospital discharge but before 90 days. VFDs and ICU-free days at 28 days were not statistically different, but surfactant subjects had significantly fewer hospital-free days (10.5 ± 7.7 vs 7.0 ± 7; $p = 0.01$). Multivariable regression adjusting for age, gender, risk strata, immune status, fluid balance, and PRISM score did not explain this difference (adjusted difference 3.5 d, $p = 0.017$). PICU categorical outcomes were not different. Neither ventilator nor fluid management differed between placebo and surfactant groups. Despite the conservative fluid management protocol, on average subjects accumulated nearly 2 L/M^2 over the first 7 days of the trial, and there was no difference between surfactant and placebo groups. Ventilator management was also comparable. Ventilator tidal volumes exceeded 8 mL/kg at least once in 58% of surfactant subjects and 57% of placebo subjects; ventilator peak pressures

TABLE 1. Demographic Comparisons Between Surfactant and Placebo[a]

Demographic Data	All ($n = 109$)	Placebo ($n = 53$)	Surfactant ($n = 56$)
Average age, yr	6.2 ± 5.9	6.0 ± 5.8	6.3 ± 6.0
Male gender (%)	56 (51)	28 (53)	28 (50)
Primary diagnosis (%)			
Viral pneumonia	52 (47)	25 (47)	27 (48)
Bacterial pneumonia	23 (22)	10 (19)	13 (23)
Aspiration pneumonia	17 (15)	9 (17)	8 (14)
Near drowning	6 (5)	2 (4)	4 (7)
Other	11 (10)	7 (13)	4 (7)
Pediatric Risk of Mortality scores	10.9 ± 7.1	10.6 ± 6.3	11.3 ± 7.8
Risk level (%)			
High	35 (32)	16 (30)	19 (34)
Low	74 (68)	37 (70)	37 (66)
Immune compromised (%)	11 (11)	4 (8.0)	7 (12)
Influenza A (%)	20 (18.3)	11 (20.7)	9 (16)
H1N1 strain (%)	14 (12.8)	9 (17)	5 (9)

[a]±SD, as appropriate.

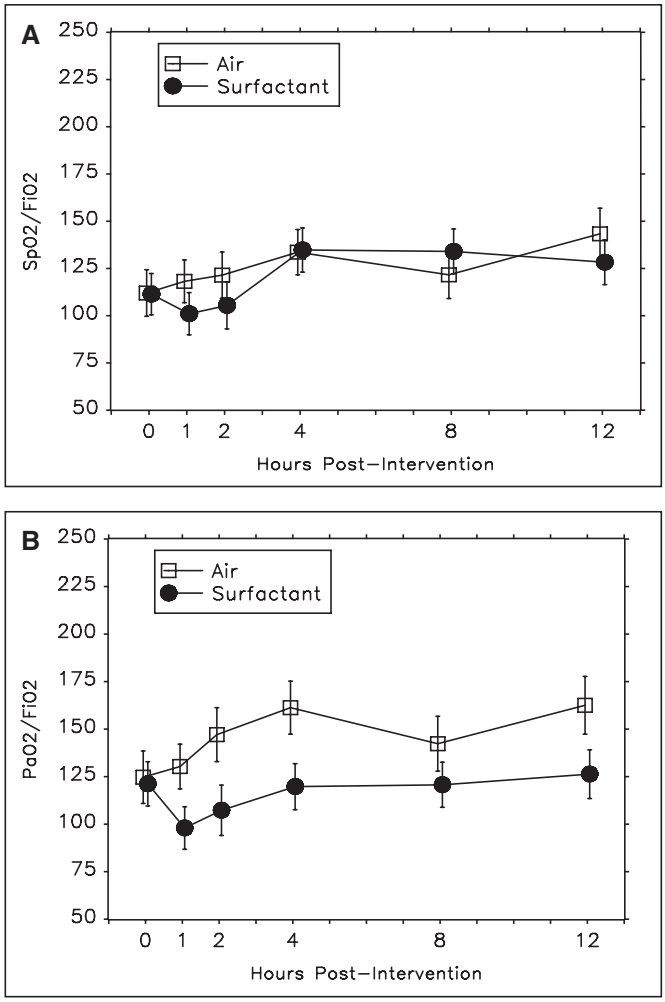


Figure 4. Change in oxygenation after intervention: **A**, change in Pao_2/Fio_2 ratio when Pao_2 is estimated from Spo_2 (using Pao_2/Fio_2 ratio = [0.443 × Spo_2/Fio_2 ratio] / [1 − 0.00232 × Spo_2/Fio_2 ratio] when $Spo_2 > 80\%$ but $< 97\%$ [16]) ($n = 45$ for both groups); **B**, change in Pao_2/Fio_2 when the Pao_2 value was available ($n = 33$ placebo, $n = 36$ surfactant).

exceeded 30 cm H_2O in 52% of surfactant subjects and 55% of placebo subjects.

DISCUSSION

Unlike our previous studies, there appeared to be no benefit from surfactant administration. The lack of immediate improvement in oxygenation after surfactant administration was unexpected since this was a consistent finding in each of our three previous studies (10–12). Although hospital-free days was the only statistically significant difference, the data also suggest that duration of ventilation and the need for PICU care may have been prolonged by surfactant treatment. The lack of acute benefit was particularly surprising because only a subgroup of ALI/ARDS subjects, those with "direct" lung injury, were included in this trial. This is the subgroup from our previous study that on post hoc analysis appeared to benefit most from calfactant (12).

Our results of our calfactant trials in children have followed a path similar to that of the adult trials. After an initial negative trial of nebulized artificial surfactant (colfosceril palmitate, Exosurf) by Anzueto et al (17), Gregory et al (18) reported improved oxygenation in a subgroup of adults with sepsis-induced ALI/ARDS using a natural surfactant (beractant, Survanta). A larger randomized controlled trial (RCT) using a recombinant surfactant containing surfactant protein C (Venticute) demonstrated improved oxygenation but no overall improvement in outcomes (19). However, on post hoc analysis, the subgroup of subjects with direct lung injury had improved mortality. This prompted the investigators to proceed with a similar RCT focused on subjects with direct lung injury, but this study was stopped for futility (20). The authors commented that their surfactant may have been inactivated by their preparation method, but no subsequent trials are currently planned. Finally, again after initial success in a smaller pilot study, the trial by Kesecioglu et al (21) using a porcine surfactant (HL-10) was stopped after the first interim analysis due to significant peridosing hypoxia and hypotension.

In this current trial with calfactant, there were three changes which, in retrospect, could have diminished the effectiveness of the treatment: 1) 60 mg phospholipid/mL rather than 35 mg phospholipid/mL calfactant preparation was used; 2) the instillation protocol did not include a lung recruitment maneuver; and 3) the instillation was performed in two rather than four aliquots with only two position changes rather than the four previous position changes (right side, head up, and head down; left side, head up, and head down). Each of these changes may have affected the distribution of the administered surfactant.

A more concentrated surfactant (60 mg/cc phospholipid vs 35 mg/cc) was used in this trial to decrease the liquid load on the lung from surfactant instillation. This was a concern for the adult study where the previous more dilute concentration would have necessitated as much as 200 cc of fluid surfactant which we feared might be associated with significant destabilization. In the interest of using a consistent protocol, this concentration was adopted for the pediatric arm as well. A lower liquid volume, however, may compromise surfactant distribution; larger surfactant volumes have been shown to have better distribution in experimental studies (22–24).

The administration of the drug without a "recruitment maneuver" was another difference in this study protocol. Given the lack of experience with surfactant administration in adults, this was thought to be a simpler, more consistent, and safer approach than taking the subject off the ventilator and "hand ventilating" using higher pressures to deliver the surfactant, as we had in previous studies (10–12). The investigators adopted this for the pediatric protocol in the interest of, again, having a uniform approach for both children and adults. Recruitment maneuvers alone have been reported to transiently improve oxygenation but with little sustained effect (25–27). In our previous study, when subjects were hand ventilated at 10 cm H_2O pressure above their ventilator peak pressure during instillation, both surfactant and placebo subjects demonstrated improved oxygenation, but the improvement was sustained only in the surfactant group (11). It is not established whether surfactant distribution is affected by a

TABLE 2. Study Outcomes

Outcomes	Placebo ($n = 53$)	Surfactant ($n = 56$)	p
Mortality	5 (9.4%)	7 (12.2%)	0.76
Ventilator-free days at 28 d[a]	17.1 ± 8.0	14.1 ± 9.3	0.08
PICU-free days at 28 d[a]	14.8 ± 8.1	10.6 ± 9.2	0.13
Hospital free days at 28 d[a]	10.4 ± 7.8	6.4 ± 7.8	0.01
Categorical ICU outcomes			0.1
Discharged on no oxygen	28	16	
Discharged on oxygen only	20	30	
Discharged on ventilator	2	1	
Died	3[b]	7	
Not discharged at 90 d	0	1	
Unknown	0	1	
Tracheostomy	4	3	0.64
Use of nitric oxide	8	6	0.57
Median fluid balance/M^2 day 7	1190	1177	0.21

[a]±SD.

[b]Two subjects died after discharge but before 90 d.

recruitment maneuver, but Lu et al (28) reported that instillation of porcine surfactant (HL-10) produced increased lung aeration relative to placebo as demonstrated by CT scan 7 days after surfactant administration. During their administration, they performed a recruitment maneuver by increasing tidal volume to 12 mL/kg predicted body weight and positive end-expiratory pressure by 5 cm H_2O for 30 minutes after instillation. In future studies, it would be of interest to investigate surfactant distribution when instilled with and without such a recruitment maneuver.

The final difference involved positioning during surfactant administration. Positioning theoretically enables gravity to assist in the distribution of the administered surfactant. This study included both children and adults, and the investigators were concerned that maneuvering larger adult subjects into four different positions might be technically difficult, would require more time, and might incur some risk. These have generally not been concerns in pediatric studies. All three of these changes may have resulted in poorer surfactant distribution. Exogenous surfactant is not likely to have an effect if it does not reach areas of the lung in which it is deficient or inhibited.

Entities, such as ALI/ARDS, which have multiple etiologies and a wide spectrum of concurrent medical issues are difficult targets for drug therapy. Improvements in supportive care have significantly improved patient outcomes, leaving fewer patients at risk for the efficacy endpoint of death. The unprecedented low mortality of the children in the placebo group in this trial made identification of a mortality benefit from lung surfactant unlikely. The lack of improvement in oxygenation observed in our previous studies may indicate that continuing advancements in supportive care for respiratory failure patients have made potential benefits of exogenous surfactant therapy moot.

We were heartened by the low mortality (11%) in the study population despite the relative severity of lung injury. This is considerably better than the 27% mortality in our previous study although the population of this study had somewhat lower average PRISM scores and Pao_2/Fio_2 ratios at entry compared with the previous population (12).

CONCLUSIONS

Calfactant instillation in pediatric patients with direct ALI did not improve oxygenation or longer term outcomes and was associated with prolonged hospital stay. Lack of benefit in this study relative to our previous studies may reflect differences in the study protocol which affected surfactant distribution. Future investigation should evaluate the effect of surfactant concentration and volume, patient positioning during administration, and recruitment maneuvers on surfactant distribution. Based on the results of this study, we cannot recommend administration of exogenous surfactant in patients with ALI/ARDS.

REFERENCES

1. Jobe AH, Ikegami M: Surfactant and acute lung injury. *Proc Assoc Am Physicians* 1998; 110:489–495
2. Wang Z, Holm BA, Matalon S, et al: Surfactant activity and dysfunction in lung injury. *In*: Lung Injury: Mechanisms, Pathophysiology, and Therapy. Notter RH, Finkelstein JN, Holm BA (Eds). Boca Raton, FL: Taylor Francis Group, 2005, pp 297–352
3. Holm BA, Wang Z, Notter RH: Multiple mechanisms of lung surfactant inhibition. *Pediatr Res* 1999; 46:85–93
4. Wright TW, Notter RH, Wang Z, et al: Pulmonary inflammation disrupts surfactant function during P. carinii pneumonia. *Infect Immun* 2001; 69:758–764
5. Günther A, Siebert C, Schmidt R, et al: Surfactant alterations in severe pneumonia, acute respiratory distress syndrome, and cardiogenic lung edema. *Am J Respir Crit Care Med* 1996; 153:176–184

6. Veldhuizen RA, McCaig LA, Akino T, et al: Pulmonary surfactant subfractions in patients with the acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1995; 152(6 Pt 1):1867–1871
7. Pison U, Seeger W, Buchhorn R, et al: Surfactant abnormalities in patients with respiratory failure after multiple trauma. *Am Rev Respir Dis* 1989; 140:1033–1039
8. Gregory TJ, Longmore WJ, Moxley MA, et al: Surfactant chemical composition and biophysical activity in acute respiratory distress syndrome. *J Clin Invest* 1991; 88:1976–1981
9. Jobe AH: Pulmonary surfactant therapy. *N Engl J Med* 1993; 328:861–868
10. Willson DF, Jiao JH, Bauman LA, et al: Calf lung surfactant extract in acute hypoxemic respiratory failure in children. *Crit Care Med* 1996; 24:1316–1322
11. Willson DF, Bauman LA, Zaritsky A, et al: Instillation of calf lung surfactant extract (calfactant) is beneficial in pediatric acute hypoxemic respiratory failure. *Crit Care Med* 1999; 27:188–195
12. Willson DF, Thomas NJ, Markovitz BP, et al: Effect of exogenous surfactant (calfactant) in pediatric acute lung injury: A randomized controlled trial. *JAMA* 2005; 293:470–476
13. Bernard GR, Artigas A, Brigham KL, et al: The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med* 1994; 149(3 Pt 1):818–824
14. ARDS Clinical Trials Network: The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000; 342:1301–1308
15. Wiedemann HP, Wheeler AP, Bernard GR, et al: Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med* 2006; 354: 2564–2575
16. Khemani RG, Thomas NJ, Venkatachalam V, et al. Comparison of SpO2 to PaO2 based on markers of lung disease severity for children with acute lung injury. *Crit Care Med* 2012; 40:1309–1316
17. Anzueto A, Baughman RP, Guntupalli KK, et al: Aerosolized surfactant in adults with sepsis-induced acute respiratory distress syndrome. *N Engl J Med* 1996; 334:1417–1421
18. Gregory TJ, Steinberg KP, Spragg R, et al: Bovine surfactant therapy for patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1997; 155:1309–1315
19. Spragg RG, Lewis JF, Walmrath HD, et al: Effect of recombinant surfactant protein C-based surfactant on the acute respiratory distress syndrome. *N Engl J Med* 2004; 351:884–892
20. Spragg RG, Taut FJ, Lewis JF, et al: Recombinant surfactant protein C-based surfactant for patients with severe direct lung injury. *Am J Respir Crit Care Med* 2011; 183:1055–1061
21. Kesecioglu J, Beale R, Stewart TE, et al: Exogenous natural surfactant for treatment of acute lung injury and the acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2009; 180: 989–994
22. Gilliard N, Richman PM, Merritt TA, et al: Effect of volume and dose on the pulmonary distribution of exogenous surfactant administration to normal rabbits or to rabbits with oleic acid lung injury. *Am Rev Respir Dis* 1990; 141:743–747
23. Davis JM, Russ GA, Metlay L, et al: Short-term distribution kinetics of intratracheally administered exogenous lung surfactant. *Pediatr Res* 1992; 31:445–450
24. Segerer H, Van Gelder W, Angenent FWM, et al. Pulmonary distribution and efficacy of exogeneous surfactant in lung-lavaged rabbits are influenced by the instillation technique. *Pediatr Res* 1993; 34:490–494
25. Fan E, Wilcox ME, Brower RG, et al: Recruitment maneuvers for acute lung injury: A systematic review. *Am J Respir Crit Care Med* 2008; 178:1156–1163
26. Gattinoni L, Caironi P, Cressoni M, et al: Lung recruitment in patients with the acute respiratory distress syndrome. *N Engl J Med* 2006; 354:1775–1786
27. The ARDS Clinical Trials Network. Effects of recruitment maneuvers in patients with acute lung injury and acute respiratory distress syndrome ventilated with high positive end-expiratory pressure. *Crit Care Med* 2003; 31:2592–2597
28. Lu Q, Zhang M, Girardi C, et al: Computed tomography assessment of exogenous surfactant-induced lung reaeration in patients with acute lung injury. *Crit Care* 2010; 14:R135

APPENDIX 1. Participating Hospitals and Collaborators

Participating Hospitals	Primary Investigator	Research Assistant
Asan Medical Center Seoul, South Korea	Lim Chae-Man, MD	
Texas Children's Hospital Houston, TX	Laura Loftis, MD	Ursula Kyle
British Columbia Children's Hospital Vancouver, Canada	David Wensley, MD	Gordon Krahn
Westmead Children's Hospital Sydney, Australia	Marino Festa, MD	Evette Gorey
Children's Hospital of Wisconsin Milwaukee, WI	Michael Quasney, MD	Kathy Murkowski
Cincinnati Children's Hospital Cincinnati, OH	Susan Poynter, MD	Marie Monaco
Morgan Stanley Children's Hospital New York City, NY	Kathy Biagas, MD	Naresh Talathoti

(*Continued*)

APPENDIX 1. (*Continued*). Participating Hospitals and Collaborators

Participating Hospitals	Primary Investigator	Research Assistant
Weill Cornell Children's Hospital New York City, NY	Steven Pon, MD	Charlene Correa
Arnold Palmer Hospital for Children Orlando, FL	Aaron Godshall, MD	Corina Mattix
Haemek Medical Center Afula, Israel	Amiran Lev, MD	Shibili Arshed
Inova Fairfax Hospital for Children Fairfax, VA	Keith Dockery, MD	Kathy Huddleston
Jackson Memorial Hospital Miami, FL	Gwenn McLaughlin, MD	Andrea Castelblanco
Nationwide Children's Hospital Columbus, OH	Margaret Chase, MD	Patsy Guittar
Children's Hospital & Medical Center, University of Nebraska Omaha, NE	Ed Truemper, MD	Machelle Zink
PennState Hershey M.S. Hershey Medical Center Hershey, PA	Neal Thomas, MD	Jennifer Stokes
Princess Margaret Hospital Perth, Australia	Simon Erickson, MD	Pania Falconer
Riley Children's Hospital Indianapolis, IN	Kris Bysani, MD	Terry Barclay
Royal Children's Hospital Melbourne, Australia	Warwick Butt, MD	Carmel Delzoppo
Royal Darwin Hospital Darwin, Australia	Dianne Stephens, MD	Jane Thomas
Starship Children's Hospital Auckland, New Zealand	John Beca, MD	Hannah Stapelton
Ste. Justine Children's Hospital Montreal, Canada	Philippe Jouvet, MD	Nicole Poitras
Shands Hospital for Children Gainesville, FL	Irina Ten, MD	Melissa Lamb
UVA Children's Hospital Charlottesville, VA	Doug Willson, MD	Christine Traul, MD
Women's and Children's Hospital Adelaide, Australia	Michael Yung, MD	Cathy Lyon