CALIPSO: A RANDOMIZED CONTROLLED TRIAL OF CALFACTANT FOR ACUTE LUNG INJURY IN PEDIATRIC STEM CELL AND ONCOLOGY PATIENTS.

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Highlights

- Pediatric Acute Respiratory Distress Syndrome (PARDS) has a high mortality
- Data do not support calfactant for children with leukemia/lymphoma/HCT and PARDS
- Allogeneic HCT patients with PARDS have higher mortality than other groups
- Conducting research among these children is challenging but necessary

Abstract

Objective: To assess if calfactant reduces mortality among children with leukemia/lymphoma or following hematopoietic cell transplantation (HCT) with pediatric acute respiratory distress syndrome (PARDS)

Design: Multicenter, randomized, placebo-controlled, double-blinded trial

Setting: Seventeen pediatric intensive care units (PICU) of tertiary care children's hospitals

Patients: Patients age 18 months to 25 years with leukemia/lymphoma or having undergone HCT who required invasive mechanical ventilation for bilateral lung disease with an oxygenation index (OI) >10 and < 37.

Interventions: Intratracheal instillation of either calfactant or air placebo (one or two doses)

Measurements and Main Results: Forty-three subjects were enrolled between November, 2010 and June 2015; 26 assigned to calfactant and 17 to placebo. There were no significant differences in the primary outcome, which was survival to PICU discharge (Adjusted Hazard Ratio of mortality for calfactant vs. placebo (95% CI): 1.78 (0.53, 6.05); p=0.35), OI, functional outcomes, or ventilator free days, adjusting for risk strata and PRISM score. Despite the risk-stratified randomization, more allogeneic HCT patients received calfactant (76% and 39%, respectively) due to low recruitment at various sites. This imbalance is important because, independent of treatment arm, and while adjusting for PRISM score, those with allogeneic HCT had a non-significant higher likelihood of death at PICU discharge (Adjusted Odds Ratio (95% CI): 3.02 (0.76, 12.06); p=0.12). Overall, 86% of the patients who survived to PICU discharge also were successfully discharged from the hospital.

Conclusions: These data do not support the use of calfactant among this high mortality group of pediatric leukemia/lymphoma and/or HCT patients with PARDS to increase survival. In spite of

poor enrollment, allogeneic HCT patients with PARDS appeared to be characterized by higher mortality than even other high-risk immunosuppressed groups. Conducting research among these children is challenging but necessary, as survival to PICU discharge usually results in successful discharge to home.

Introduction

The recently convened Pediatric Acute Lung Injury Consensus Conference (PALICC) (1, 2), along with others (3-8), have highlighted differences in outcomes from Pediatric Acute Respiratory Distress Syndrome (PARDS) in children with immunosuppressive diseases compared to those with a functional immune system. Historically, acute lung injury in these children has been associated with worse survival, particularly among the hematopoietic cell transplantation (HCT) population with mortality rates of up to 60% (7-13). Until recently these children have been excluded from interventional trials evaluating therapeutic interventions for respiratory failure (6). However, given this unacceptably high mortality, the prevalence of respiratory failure among these children (7, 14), their relatively large contribution to pediatric intensive care unit (PICU) admissions (12, 13, 15, 16), and their significant decline in functional status after critical illness (17), prospective interventional research among this patient population is warranted.

Exogenous surfactant preparations have been successful in treating and preventing neonatal respiratory distress syndrome (18-20), and are now considered standard of care. However, efficacy in older children and adults has been variable (6, 21-24). A 21-center trial of intratracheal calfactant installation in children with PARDS demonstrated improved survival relative to placebo (6). Moreover, a *post-hoc* analysis suggested a potential benefit of calfactant in immunocompromised children with acute respiratory failure characterized by an oxygenation index (OI) between 13 and 37 (25).

Encouraged by these results, a double-blinded, randomized, controlled multicenter trial was designed to evaluate the efficacy of calfactant relative to placebo in reducing mortality in

immunosuppressed children with leukemia/lymphoma or following HCT for any indication with PARDS.

Methods

Patient Recruitment

Seventeen PICUs from the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network enrolled patients (see Appendix). The protocol was reviewed and approved by each institutional review board (IRB) and informed consent was obtained prior to randomization. The study was registered on ClinicalTrials.gov (NCT00999713).

Entry criteria included age 18 months to 25 years, a diagnosis of leukemia/lymphoma or having undergone HCT for any indication, intubation and mechanical ventilation, radiographic evidence of bilateral lung disease, presence of an arterial catheter, and an OI >10 and < 37 (OI = FiO_2 x Mean Airway Pressure x 100 / Partaial pressure of oxygen from an arterial blood gas) for two consecutive blood gases separated by at least one hour within 48 hours of endotracheal intubation (this was extended to 72 hours after 24 patients had been enrolled). The OI criteria (25) were intended to identify a patient population likely to experience a survival benefit by excluding those with minor lung injury expected to survive irrespective of therapy, as well as those with such severe disease that survival was improbable. Exclusion criteria included chronic lung disease, status asthmaticus, brain death, uncorrected congenital heart disease, myocardial dysfunction, pulmonary edema from clinically evident cardiac failure (in the event that cardiac disease is suspected, this was excluded by echocardiography), severe neurological injury, airway anomalies or if care was electively limited. Additionally, potential subjects were excluded if they required the use of continuous, non-invasive positive airway pressure (CPAP) or BiLevel positive airway pressure (BiPAP) ventilation for > 168 hours (7 days) at any level, or if they had

received non-invasive ventilation for > 72 hours with any of the following settings: FiO_2 > 0.60, CPAP > 8 cmH_2O or IPAP > 24 cmH_2O.

Randomization was stratified by institution and the presence of an allogeneic HCT prior to study entry (10, 12, 15) in an effort to balance the risk of mortality between the two treatment groups (calfactant and placebo). Patients were recruited between November, 2010 and June 2015.

Study Protocol

Subjects were randomized to receive either intratracheal installation of two doses of calfactant or air placebo. Initially, the protocol specified a calfactant concentration of 60 mg/mL of phospholipid in concert with the Calfactant in the Acute Respiratory Distress Syndrome (CARDS) study (ClinicalTrials.gov: NCT00682500) (26, 27). After seven subjects had been enrolled and the CARDS trial completed, the calfactant concentration was changed back to the original concentration of 35 mg/mL phospholipid with Food and Drug Administration (FDA) and IRB approvals [6]. The protocol mandated a second dose of calfactant be given 12 (+/- 2) hours after the initial treatment only if the patient remained intubated and on mechanical ventilation with an OI > 10 or if the patient experienced at least a 25% decrease in OI. The volume of calfactant for a child weighing $\leq$ 10 kg was 3 mL/kg and 80 mL/M2 body surface area for children over 10 kg. Calfactant was initially administered in two equal aliquots, but changed to four aliquots as previously described (6), after a review of the CARDS trial data.

Each participating pharmacy was provided a randomization log. To maintain blinding, the pharmacist delivered an opaque container to the PICU containing either the study drug or an air-filled syringe and handed it directly to the administrator of the intervention, a trained professional who was not involved in the daily care of the patient. The endotracheal tube was

covered with opaque tape and the intervention was completed behind a barrier, allowing physicians, investigators, and other healthcare personnel caring for the patient to remain blinded throughout the study.

In addition to the qualifying blood gases, arterial blood gases were obtained at baseline prior to intervention and at a minimum of three time points after the intervention (1, 4 and 12 hours). Investigators agreed to follow ventilator recommendations which consisted of a low tidal volume/open lung strategy and permissive hypercapnia, with the goal of adequate oxygenation and ventilation. These recommendations were based on a previous PALISI network study of prone positioning (28).

Study Drug

Calfactant (provided by ONY Inc, Amherst, NY) is a modified natural calf lung surfactant approved by the US FDA for neonatal respiratory distress syndrome. It is produced by saline lavage of calf lung and subsequent extraction of the phospholipids, neutral lipids, and hydrophobic apoproteins SP-B and SP-C.

Study Outcomes

The primary outcome was survival from PICU admission to PICU discharge. Secondary outcomes included changes in oxygenation after dosing, ventilator free days (VFD; the number of days alive and free of invasive mechanical ventilation at 28 days), the proportion of patients requiring retreatment, and changes in Pediatric Outcome Performance Category (POPC) and Pediatric Cerebral Performance Category (PCPC) scores (29). Given the established worse outcomes from respiratory failure among allogeneic HCT patients (10), and the ability of Pediatric Risk of Mortality (PRISM) scores to discern mortality (30), these covariates were controlled for when appropriate in analyses.

Adverse events around the time of drug or placebo administration were considered safety outcomes and included oxygen desaturation (< 80% for > 60 seconds), bronchospasm requiring bronchodilator therapy, air leak, hypotension, and / or bradycardia, and any clinical change in the patient deemed significant or requiring additional therapy deemed related to the intervention. Serious adverse events, including death, were collected and reviewed by the independent data safety monitoring board (DSMB).

Study Management

Sample size calculations were based on previous work (25) which demonstrated that 33% of calfactant-treated patients died prior to PICU discharge as compared to 71% of placebo patients. Using selective OI entry criterion, stratifying based on the presence of allogeneic HCT, and accepting the 27% difference in mortality between the two treatment groups observed in the *post-hoc* analysis, it was estimated that 63 patients would be required in each study arm to demonstrate an effect of calfactant on mortality with 85% power in this patient population at the 0.05 significance level. Therefore, a total sample size of 140 subjects (70 in each arm) was targeted based on an estimate that 10% of patients would withdraw or have missing data.

An interim analysis was planned after the first 70 patients were enrolled, with defined stopping rules for both efficacy and futility. Enrollment in the study was voluntarily halted for approximately nine months after the CARDS study (26, 27) was completed, in order to determine the impact of the CARDS study data on the present protocol. After review of the CARDS study data, protocol modifications were proposed and approved by the FDA and IRB prior to re-opening the trial to subject accrual. These modifications involved reverting to the treatment protocol used in the original multicenter pediatric calfactant randomized controlled trial (6), which included using the less concentrated formulation of calfactant and administering

the medication in four aliquots rather than two. Due to poor enrollment after nearly five years of study, the interim analysis was conducted after the enrollment of only 43 patients. Based on that analysis, the DSMB elected to terminate the study because of the poor enrollment and lack of evidence of efficacy.

Statistical Analysis

Cox proportional hazards regression was used to assess the differences between treatment groups for the primary clinical outcome of survival from PICU admission to PICU discharge, while controlling for the risk strata and PRISM score measured at the time of PICU admission. A total of 20 patients died prior to discharge, 22 were censored (alive at the time of discharge), and one was excluded during analysis due to a missing PRISM score. The Cox proportional hazards assumption was assessed using the supremum test (31).

Binary logistic regression models, adjusting for risk strata and PRISM score at the time of PICU admission, were used to evaluate differences between groups for those requiring retreatment (e.g. a second intervention after 12 hours), and those experiencing no change or experiencing improvement in their POPC/PCPC scores between PICU admission and hospital discharge. In evaluating the proportion requiring retreatment, three patients were excluded in assessment of this outcome, as two patients did not receive the first intervention (therefore making them ineligible to receive a second intervention) and one patient was missing a PRISM score. It is worth noting that all patients had the opportunity to be retreated, meaning that no deaths were experienced prior to the assessment for retreatment (within the 12-hour time window). The difference in POPC/PCPC scores was defined as the hospital discharge score minus the PICU admission score. Therefore, a difference of zero or less than zero was indicative of no change or an improvement, respectively.

A general linear model with correlated errors (32) was used to analyze the repeated measurements of OI over the 12 hours (i.e., 0, 1, 4, and 12 hours) following the first and second interventions. A natural log transformation of the response was necessary to satisfy the normality assumption of the model; therefore, geometric means are reported. The interaction of the treatment group over time was assessed, while controlling for risk strata.

Differences in the number of VFDs were analyzed using a zero-inflated Poisson (ZIP) model with a log link function due to a large number of zero ventilation free days. One patient was excluded due to a missing PRISM score. An unsuccessful extubation was defined as death prior to extubation or on ventilation for longer than 28 days. An extubation was only considered successful if the subject remained extubated for > 48 hours. If a subject was not successfully extubated according to these criteria, they were classified as having zero VFDs. If a subject was successfully extubated, the number of VFDs was calculated as the difference between 28 days and the number of days that the subject was on a ventilator. There was one instance where a subject was extubated and then re-intubated. In this case, the number of VFDs was calculated manually. The initiation point for ventilation was defined as the date and time of the pre-intervention qualifying OI. The stopping point was the date and time of extubation. All hypothesis tests were two-sided and a significance level of 0.05 was considered significant. All analyses were performed using SAS software, version 9.4 (SAS Institute Inc., Cary, NC) and figures were generated using R software (The R Foundation, Vienna, Austria).

Results

A total of 43 subjects were consented and randomized. 26 subjects were assigned to the calfactant group, and 17 were assigned to the placebo group (Figure 1). Two subjects assigned to the calfactant group did not receive any treatment (one died after randomization but before treatment secondary to pulmonary hemorrhage, and the other worsened and was withdrawn by the clinical team), but are included as per intention-to-treat planned analyses. Both groups met criteria for severe PARDS at study entry, with similar mean OI values between groups [Mean (SD): 21.9 (12.2) Drug vs. 22.6 (12.1) Placebo]. (Table 1). Demographics, severity of illness, and cause of lung injury also appeared similarly distributed between the two treatment groups (Table 1). Of the 18 subjects who were stratified to the leukemia/lymphoma/autologous HSCT group, 7 had undergone HSCT.

After adjusting for risk strata and PRISM score, there was no difference in survival at the time of PICU discharge. Those who received calfactant were more likely (Adjusted Hazard Ratio (95% CI): 1.78 (0.53, 6.05); p=0.35; Table 2 and Figure 2) to experience death compared to the placebo group; however, this was not statistically significant. The median survival time for the calfactant group was 42 days, while the median survival time for the placebo group was 58 days (Figure 2).

Despite stratifying based on risk strata, the unexpectedly small number of subjects recruited at each study site and the size of the randomization blocks resulted in a larger proportion of the 25 allogeneic HCT patients receiving calfactant versus placebo (76% and 39%, respectively) (Table 1). Allogeneic HCT patients tended to be characterized by higher mortality irrespective of treatment allocation. Fifteen of the 25 (60%) allogeneic HCT patients died prior to PICU discharge as compared to only 33% (6/18) of the leukemia/lymphoma and autologous

HCT patients (chi-square test p = 0.08). Even after adjusting for PRISM score, allogeneic HCT patients were 3 times as likely (Adjusted Odds Ratio (95% CI): 3.02 (0.76, 12.06); p=0.12) to die prior to PICU discharge compared to the non-transplant and autologous HCT patients. Although this difference was not statistically significant, allogeneic HCT patients were characterized by a five-fold increase in their odds of death at the time of hospital discharge, adjusting for PRISM score, as compared to the non-transplant and autologous HCT patients [Adjusted Odds Ratio (95% CI): 5.0 (1.3-19.6); p=0.02].

After adjusting for risk strata there was no significant difference in oxygenation as measured by OI between calfactant and placebo groups in the 12 hours after the intervention (Figure 3). Additionally, other secondary clinical outcomes including change in POPC/PCPC, VFDs, and need for retreatment at 12 hours, were not different between calfactant and placebo subjects (Table 2). A total of 22 patients survived until PICU discharge, of which 19 (86%) were successfully discharged from the hospital. Ten of 25 (40%) allogeneic HCT patients survived to PICU discharge; seven of those ten survived to hospital discharge.

Nine peri-dosing events were reported. These included three episodes of hypotension (all calfactant), five episodes of desaturation (four calfactant and one placebo) and one pneumomediastinum (calfactant. There were a total of 25 serious adverse events reported and reviewed by the DSMB. Only two were felt to be probably related to the study and both occurred during dosing in the calfactant group. One was a severe episode of desaturation without bradycardia, and one was a severe hypotensive event requiring a fluid bolus and a single dose of epinephrine.

Three protocol violations were identified: One patient was older than the allowable age (calfactant), one patient had an initial OI higher than allowed (placebo), and one patient mistakenly did not receive a second intervention despite qualifying (calfactant).

Discussion

Despite the limited enrollment, useful information to the care for this high-risk patient population can be gleaned from this study. First, in the context of the present study with the stated limitations of imbalanced enrollment, small sample size, and others, these data do not support a survival advantage with the use of intratracheal instillation of calfactant in this population of children. The overall comparison of mortality among treatment groups did not provide sufficient evidence in support of a benefit with calfactant therapy. The mortality rate of 74% at hospital discharge among the 19 calfactant-treated allogeneic HCT patients is quite comparable to the results of other contemporaneous studies of pediatric HCT patients with PARDS (9, 11, 33, 34).

Second, allogeneic HCT patients with PARDS appear to have significantly worse outcomes compared to other immunosuppressed populations including leukemia/lymphoma and autologous HCT patients. These findings are consistent with previously published results (10, 12, 15). Possible reasons include intensive conditioning regimens, baseline organ dysfunction, more aggressive malignant disease, and perhaps most notably, a dysregulated (rather than simply suppressed) immune system. While the data collection was limited, and we do not have access to data related to the time from HCT to the onset of PARDS, this is an issue which is likely important in the design of future research. Regardless of the cause, this finding is most relevant

to the design of future studies of PARDS enrolling children with cancer and/or who have undergone HCT.

Third, the study demonstrates that most children who survive their acute episode of PARDS survive to hospital discharge. In this study, a total of 22 patients survived until PICU discharge, of which 19 (86%) were successfully discharged from the hospital. With respect to the 25 allogeneic HCT patients, 10 (40%) survived until PICU discharge, seven of which also survived to hospital discharge. These findings add to the growing body of literature suggesting that recovery from PARDS is likely to result in longer term survival in HCT patients (10, 11, 33, 35). Such data support aggressive treatment of PARDS in these children and affirm the need for further research to improve their acute outcomes. Moreover, longer term functional outcomes should be considered in any study of PARDS in immune-compromised children.

Fourth, this study illustrates the difficulty of performing effective research in this population. Given the dismal prognosis of PARDS in these children, effective study is needed to advance understanding and improve outcomes. However, conducting randomized controlled trials has proven to be challenging in pediatric critical care in general (36), and particularly difficult in the immunosuppressed population. A funded study of hemofiltration in pediatric HCT patients with PARDS was closed after enrolling only 16 subjects, despite 35 participating sites over a two-year period (JV DiCarlo, personal communication). A study of etanercept in adult HCT patients with idiopathic pneumonia syndrome (IPS) was terminated for poor accrual after enrolling only 34 of the targeted 120 subjects (IPS) (35, 37). Similarly, a pediatric trial of etanercept in IPS in children undergoing stem cell transplantation enrolled only 39 subjects over a 5-year period despite 22 participating sites (37). While that study was stopped prematurely when it satisfied an established stopping rule for efficacy, the authors concluded that they were

unlikely to ever be able to perform the definitive phase III trial. However, etanercept is now used routinely in children undergoing stem cell transplantation with IPS.

The challenges to research in this field are clear. First, the overall patient population is relatively small. The Center for International Blood and Marrow Transplant Research® reported that between 2008 and 2014, 4408 children less than or equal to 18 years of age underwent a first allogeneic HCT and an additional 3076 received a first autologous transplant (38). Accepting a 25% incidence of PARDS among pediatric HCT patients (7), there are less than 2000 available patients to be studied over a comparable time period. Consequently, identifying a sufficient number of patients for study requires a large number of centers, each of which is only likely to enroll a handful of patients. This situation contributed substantially to the unequal patient distribution in the current trial, which may have influenced the results obtained. For future multi-center designed studies looking to recruit this patient population (or other cohorts with rare diseases/known recruitment difficulty), we would suggest randomizing with a fixed block size equal to the number of treatments and using as few strata as possible to account for primary confounders.. Later, possible confounders (such as study site) can be accounted for by incorporating them as random effects in applicable models. This is a particularly ideal approach when there are a large number of sites with little recruitment. An additional approach, based on the fact that an open labeled trial of etanercept (37) completed enrollment sooner than expected, while a similar randomized controlled trial in adults (35) took longer to complete, would be to utilize alternative methodology other than randomized placebo-controlled trials to attempt to overcome the issues related to randomization. With the lessons learned from this trial, and with the recommendations above, it is feasible that this patient population can undergo further study. Moreover, the patient population is extremely heterogeneous, varying by etiology of the lung

disease as well as the underlying diagnosis and other transplant-related factors, including the type of transplant, the conditioning regimen, the source of the transplant, and the presence of graft versus host disease. Therefore, identifying a well-defined patient population of adequate size for studies of this condition is most difficult.

In addition to the limited patient pool, it is a challenge to secure mutual support and true equipoise from two discordant clinical services. Many of these patients will have been previously enrolled in a clinical trial led by the transplant service and subsequent enrollment in another trial can complicate analysis of the initial study. In the current trial, contemporaneous enrollment accounted for 25% of the patients who were eligible, but not approached for enrollment. Collaboration between pediatric intensivists and oncologists in the early stages of future trial design has the potential to mitigate this concern, and the HSCT subgroup of the PALISI Network has taken this approach in recent protocol design.

Additionally, participating in research during a time of critical illness may be difficult for the parents of these children. They must agree to participate in a trial after being informed that: 1) there is a medication that may help their critically ill child, although its true efficacy remains to be determined; 2) the medication appears to be relatively well-tolerated although the potential for adverse effect is not completely established and will be assessed as part of the trial; and 3) there is no guarantee of who will receive the study medication. Although not formally studied, there were reports of parent and physician refusal to participate due to both reasons: they did not want to risk the chance of being randomized to placebo and wished to receive calfactant as an off-label clinical therapy, or they did not wish to undertake potential risks of calfactant without proven benefit. This issue was markedly similar to the study of hemofiltration in pediatric HCT patients referenced above (JV DiCarlo, personal communication). Further, all this information is

couched within the context that the primary purpose of the study is not to help their child (although that is a possibility of participation), but rather, to best inform the use of this medication for future children. Impressively, despite this most difficult of situations, 60% of families that were approached consented to participate in the study.

Conclusions

This trial does not provide sufficient evidence in support of an overall survival benefit for calfactant in this population of immune compromised children with PARDS. The results demonstrate that allogeneic HCT patients with lung injury tend to be a unique group characterized by higher mortality than other high-risk immunosuppressed groups. The trial not only highlights many of the difficulties associated with conducting research among these children, but also re-affirms the need for such study, as short-term survival appears to correlate strongly with longer term survival, as the majority of the children discharged from the PICU are successfully discharged home.

Appendix: CALIPSO Study Investigators

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Figure Legends

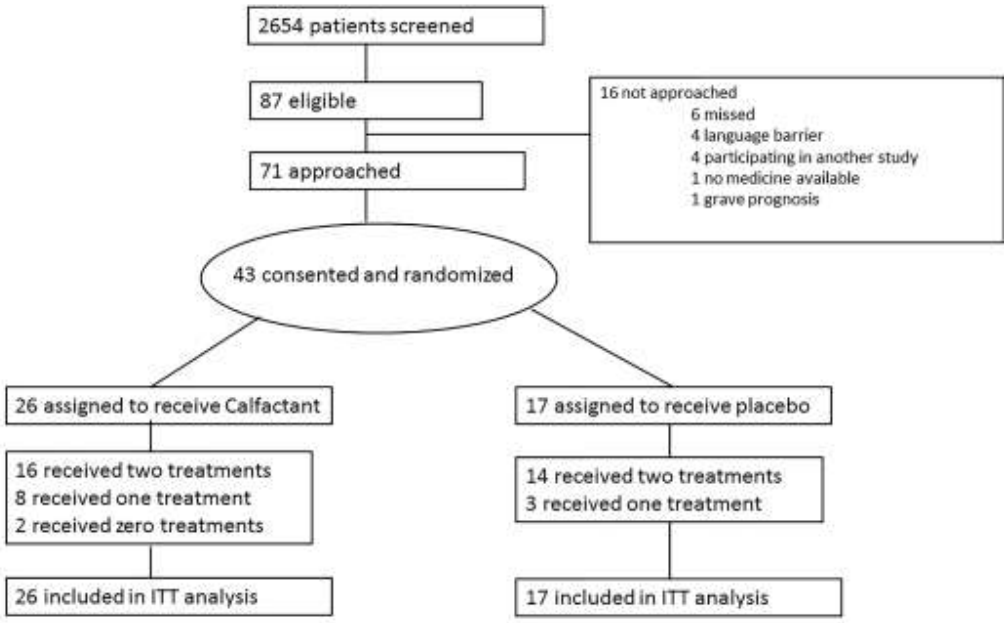

Figure 1. Patient Enrollment and Randomization. The figure depicts the CONSORT flow diagram for the trial. (ITT = Intention to Treat)

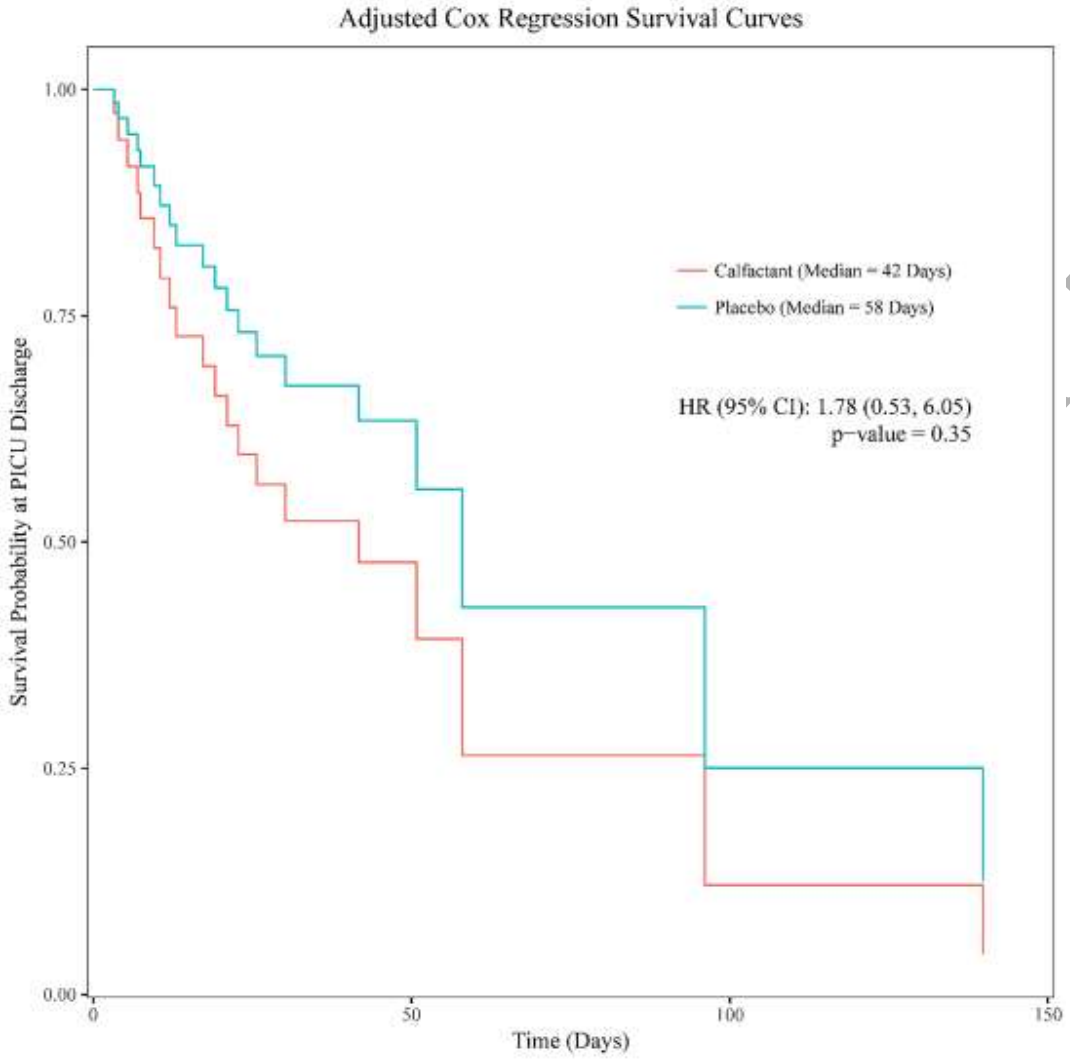

Figure 2. Figure 2. Adjusted Cox Regression Survival Curves for the Two Treatment Groups. The figure illustrates the adjusted (risk strata and PRISM score) Cox regression survival curves for the two treatment groups from PICU admission to PICU discharge. There was no significant difference in survival between the two groups.

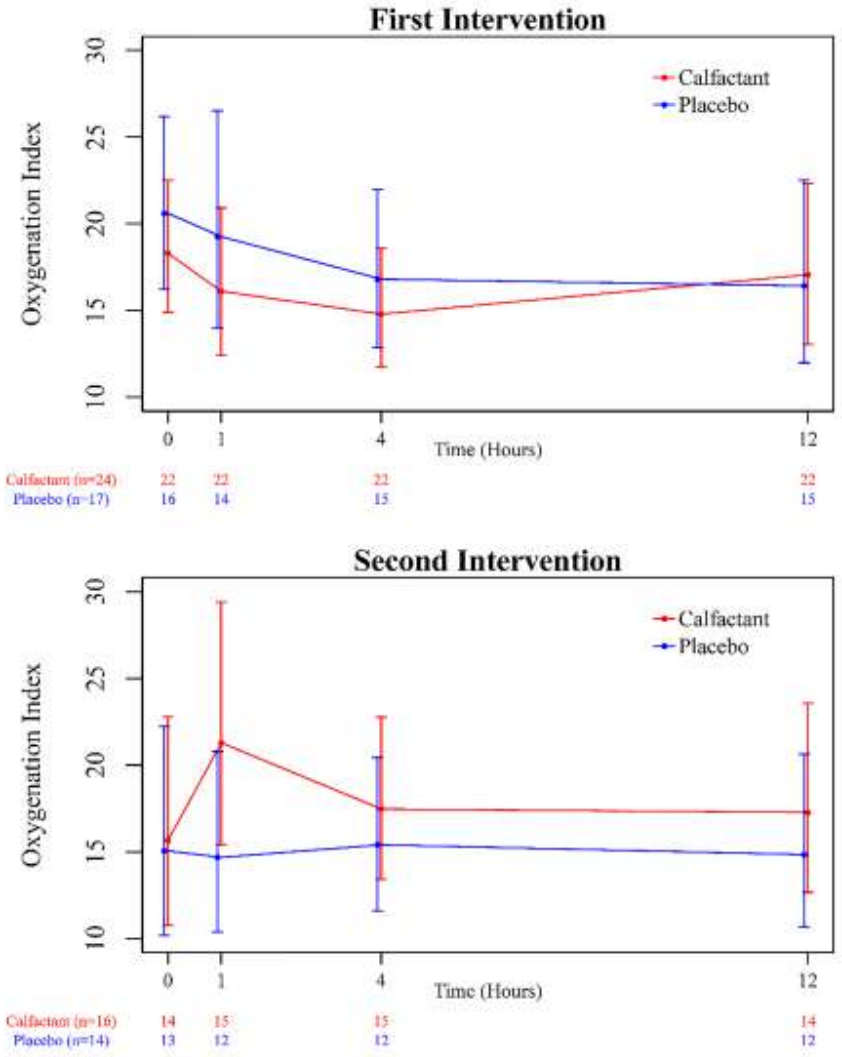

Figure 3. Comparison of Oxygenation Index at Assessed Time Points for the Two Treatment Groups. The figure illustrates the oxygenation index (OI) measured over a twelve hour time-period immediately following study intervention for both treatment groups, adjusting for risk strata. Points plotted represent geometric means and corresponding 95% confidence intervals at each data collection time point. There were no significant differences between the treatment groups with respect to Oxygenation Index over time.

Table 1: Demographics, Severity, and Diagnoses at Study Entry*

Demographics		
	Calfactant (n=26)	**Placebo (n=17)**
Age (years)	12.1 (6.1)	12.8 (5.4)
Weight (kg)	45.1 (23.3)	50.1 (28.7)
Height (cm)	142.2 (33.6)	146.2 (29.3)
BSA (m^2)	1.3 (0.5)	1.4 (0.5)
Sex		
Male	16 (61.5%)	12 (70.6%)
Female	10 (38.5%)	5 (29.4%)
Race (if known)		
American Indian/Alaska Native	1 (4.4%)	0 (0.0%)
Black or African American	5 (21.7%)	2 (12.5%)
White	16 (69.6%)	14 (87.5%)
More Than One Race	1 (4.4%)	0 (0.0%)
Ethnicity (if known)		
Hispanic or Latino	7 (31.8%)	8 (50.0%)
Not Hispanic or Latino	15 (68.2%)	8 (50.0%)
Severity of Illness #		
	Drug (n=26)	**Placebo (n=17)**
PRISM Score	19.8 (7.5)	16.1 (4.7)
Risk Strata		
Leukemia Lymphoma Autologous HSCT	7 (26.9%)	11 (64.7%)
Allogeneic HSCT	19 (73.1%)	6 (35.3%)
Oxygenation Index	21.9 (12.2)	22.6 (12.1)
PaO_2	77.7 (35.0)	75.1 (26.1)
pH	7.34 (0.09)	7.31 (0.11)

$PaCO_2$	51.4 (18.7)	52.8 (11.8)
Oxygen saturation	93.4 (5.3)	94.4 (4.9)
POPC		
Good	7 (29.2%)	3 (18.8%)
Mild Disability	6 (25.0%)	3 (18.8%)
Moderate Disability	7 (29.2%)	7 (43.8%)
Severe Disability	3 (12.5%)	3 (18.8%)
Coma/Vegetative State	1 (4.2%)	0 (0.0%)
PCPC		
Normal	15 (62.5%)	7 (43.8%)
Mild Disability	5 (20.8%)	4 (25.0%)
Moderate Disability	2 (8.3%)	2 (12.5%)
Severe Disability	1 (4.2%)	3 (18.8%)
Coma/Vegetative State	1 (4.2%)	0 (0.0%)

Causes of Pediatric Acute Respiratory Distress Syndrome		
	Drug (n=26)	**Placebo (n=17)**
Pneumonia	17 (65.4%)	12 (70.6%)
Viral	8 (30.8%)	2 (11.8%)
Protozoa	0 (0.0%)	0 (0.0%)
Idiopathic Syndrome	0 (0.0%)	5 (29.4%)
Fungal	2 (7.7%)	2 (11.8%)
Radiation	1 (3.9%)	0 (0.0%)
Bacterial	6 (23.1%)	2 (11.8%)
Aspiration	0 (0.0%)	1 (5.9%)
Pulmonary Hemorrhage	1 (3.9%)	4 (23.5%)
Pulmonary Graft versus Host Disease	1 (3.9%)	1 (5.9%)
BOOP	0 (0.0%)	1 (5.9%)
Other[$]	12 (46.2%)	6 (35.3%)

Abbreviations: BSA, body surface area; POPC, pediatric overall performance category; PCPC, pediatric cerebral performance category; BOOP, bronchiolitis obliterans organizing pneumonia

* Continuous Variables: Mean (SD); Categorical Variables: Frequency (Col. %)

Measures represent the pre-intervention arterial blood gas if available; otherwise the arterial blood gas upon PICU admission was utilized.

$ Other category includes sepsis, bacteremia, HHV6 without pneumonia, multi-organ dysfunction syndrome, secondary to Ara-C related inflammatory response, and others.

Table 2: Clinical outcomes comparing the differences between those subjects treated with calfactant and those who received placebo.

Clinical Outcomes	Effect Comparison (95% CI)[a]	p-value
Mortality (PICU Discharge): HR[b]	1.78 (0.53, 6.05)	0.35
First Intervention (Outcome = OI)[c] Treatment*Time Interaction	-	0.64
Second Intervention (Outcome = OI)[c] Treatment*Time Interaction	-	0.52
Deterioration in POPC Score: OR[b]	0.57 (0.11, 2.85)	0.49
Deterioration in PCPC Score: OR[b]	0.45 (0.09, 2.22)	0.33
Retreated (Received the Second Intervention): OR[b]	0.44 (0.08, 2.35)	0.34
Expected Number of Ventilation Free Days: RR[b]	1.11 (0.88, 1.41)	0.37
Unsuccessful Extubation[d]: OR[b]	0.58 (0.12, 2.77)	0.50

HR=Hazard Ratio
OR=Odds Ratio
RR=Rate Ratio
VFD=Ventilation Free Days
[a]All effects compare the calfactant group to the placebo group
[b]Adjusted for Risk Strata + PRISM Score
[c]Adjusted for Risk Strata
[d]Defined as free from mechanical ventilation for greater than 48 hours