Aerosolized Calfactant for Newborns With Respiratory Distress: A Randomized Trial

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abstract

BACKGROUND: Exogenous surfactants to treat respiratory distress syndrome (RDS) are approved for tracheal instillation only; this requires intubation, often followed by positive pressure ventilation to promote distribution. Aerosol delivery offers a safer alternative, but clinical studies have had mixed results. We hypothesized that efficient aerosolization of a surfactant with low viscosity, early in the course of RDS, could reduce the need for intubation and instillation of liquid surfactant.

METHODS: A prospective, multicenter, randomized, unblinded comparison trial of aerosolized calfactant (Infasurf) in newborns with signs of RDS that required noninvasive respiratory support. Calfactant was aerosolized by using a Solarys nebulizer modified with a pacifier adapter; 6 mL/kg (210 mg phospholipid/kg body weight) were delivered directly into the mouth. Infants in the aerosol group received up to 3 treatments, at least 4 hours apart. Infants in the control group received usual care, determined by providers. Infants were intubated and given instilled surfactant for persistent or worsening respiratory distress, at their providers' discretion.

RESULTS: Among 22 NICUs, 457 infants were enrolled; gestation 23 to 41 (median 33) weeks and birth weight 595 to 4802 (median 1960) grams. In total, 230 infants were randomly assigned to aerosol; 225 received 334 treatments, starting at a median of 5 hours. The rates of intubation for surfactant instillation were 26% in the aerosol group and 50% in the usual care group ($P < .0001$). Respiratory outcomes up to 28 days of age were no different.

CONCLUSIONS: In newborns with early, mild to moderate respiratory distress, aerosolized calfactant at a dose of 210 mg phospholipid/kg body weight reduced intubation and surfactant instillation by nearly one-half.

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WHAT'S KNOWN ON THIS SUBJECT: Surfactant therapy is only approved for administration by intubation. However, neonatal intubation can be harmful. Aerosolized surfactant can avoid intubation and may be efficacious. However, clinical trials to date have been small and mostly uncontrolled and have had mixed results.

WHAT THIS STUDY ADDS: Our large, multicenter randomized controlled trial reveals that aerosolized surfactant, by using a novel delivery device, can be readily administered, independent of the nasal respiratory support circuit, and significantly reduces the need for neonatal intubation and instillation of liquid surfactant.

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Animal-derived surfactants decrease morbidity and mortality among newborns with respiratory distress syndrome (RDS).[1–5] Early surfactant administration decreases the risk of pulmonary injury and neonatal death compared to delayed treatment.[6] Experts have suggested that treatment should begin as soon as signs of RDS appear.[7]

However, neonatal endotracheal intubation, necessary for intratracheal surfactant administration, can be difficult and harmful.[8,9] First-attempt failure rates are high[8,10] and multiple attempts are associated with complications.[11,12] Lung injury occurs more frequently in newborns requiring intubation because even brief use of positive pressure breaths starts an inflammatory cascade, leading to alveolar damage.[13–15]

Less invasive methods of surfactant administration are being studied in an effort to avoid the complications of intubation; these include using an intratracheal catheter or supraglottic airway device. Both of these methods, however, still subject the neonate to airway manipulation and/or positive pressure breaths.[16–19] Aerosol delivery of surfactant avoids manipulation of the airway and requires no technical skill.

In animal models of RDS, aerosolized surfactant improves gas exchange and lung mechanics similar to bolus instillation, with less physiologic disturbance.[20–22] Animal studies suggest more homogeneous surfactant distribution with aerosol delivery.[20,23] There have been only two small randomized controlled clinical trials (RCTs) of aerosolized surfactant; results were mixed, and the efficacy of this approach remains unclear.[24,25]

We conducted a large, multicenter RCT, comparing aerosolized surfactant to usual care in spontaneously breathing newborns with respiratory distress. We hypothesized that in newborns requiring noninvasive respiratory support for suspected or confirmed RDS, those who receive aerosolized surfactant between 1 and 12 hours of age would be less likely to require intubation for liquid surfactant administration than those who receive usual care during the first 4 postnatal days.

METHODS

In this pragmatic clinical trial, we compared aerosolized calfactant (Infasurf; ONY Biotech, Amherst, NY) to usual care in newborns with early mild to moderate respiratory distress in 22 level III or IV NICUs in the United States. Before randomization, we obtained written informed consent from each infant's parent(s) or guardian, either prenatally or shortly after birth. The protocol was approved by a national institutional review board (Western Institutional Review Board, Olympia, WA) as well as local institutional review boards, if required. The trial was monitored by an independent data and safety committee. Data analysis was conducted by an independent statistician. The completeness and accuracy of the data and analysis was assured by the sponsor's clinical trial monitors, a contract research firm (Applied Healthcare Research Management, Buffalo, NY) retained by the sponsor, and by the study statistician. All data were available to the authors, who developed the article. The authors vouch for the accuracy and completeness of the data and adherence of the trial to the protocol. The trial was registered on www.clinicaltrials.gov on February 23, 2017, before the first patient was enrolled (identifier NCT03058666).

Participants

Two cohorts were recruited with separate randomization sequences at each site. Cohort 1 were newborns who were nonintubated, had not previously received surfactant, were >1 hour but <12 hours of age, and were with suspected or confirmed RDS requiring therapeutic administration of nasal respiratory support by nasal continuous positive airway pressure (nCPAP), high-flow nasal cannula, or noninvasive ventilation. Initially, there was an entry requirement for a fraction of inspired oxygen (F_{IO_2}) concentration of 0.25 to 0.40. Four months into the trial, it was discovered that several sites were using higher positive airway pressures to minimize F_{IO_2}. Because of this practice change, the minimum F_{IO_2} requirement was removed in the fifth month of the trial. Cohort 2 were patients <24 hours of age who had received liquid surfactant by 1 hour of age and were then extubated to nasal respiratory support.

Exclusion criteria were a congenital anomaly limiting care or requiring surgery; hypotension with metabolic acidosis (a base deficit >10 mEq/L); hypoxemia (O_2 saturation <88%) or hypercapnia (arterial partial pressure of carbon dioxide [P_{aCO_2}] ≥60 mm Hg) unresponsiveness to intervention; grade 3 or 4 intraventricular brain hemorrhage; or acute hypoxic encephalopathy, defined as disturbed neurologic function, including abnormal tone and/or reflexes for gestational age, after a suspected perinatal hypoxic-ischemic event, as evidenced by a 5-minute Apgar score <5 and/or umbilical cord acidosis (pH <7.0 and/or based deficit ≥16 mmol/L).

Design

Each site was given separate sequential randomization codes in opaque envelopes. The study sponsor generated the code for each site using the Moses-Oakford algorithm. Group assignment was indicated by the next sequential envelope. Alternating blocks of size 2 and 4 were used but

not revealed to investigators. The study was unblinded.

The aerosol group received 6 mL/kg body weight of 35 mg/mL calfactant suspension, 210 mg phospholipids/kg body weight, through a modified Solarys nebulizer. The Solarys device is approved by the Food and Drug Administration for delivering drugs to intubated patients. The distal end was modified to resemble a pacifier; the tip was an inverted dome, through which the calfactant aerosol was generated. (See Supplemental Fig 8 for photographs of the modified Solarys device.) The device is seated in the mouth with the patient in the "sniffing" position and secured by using a Tortle bonnet. As per the manufacturer, the rate of delivery is 0.20 ± 0.02 mL/minute. Aerosol delivery was continuous, not synchronized with inspiration. In preclinical and pilot studies, normal fluctuations in airway pressure while receiving noninvasive support did not significantly change during aerosol delivery. Infants in the aerosol group could receive up to 3 doses during the first 72 hours of age. Repeat dosing required a positive response to the previous dose (a reduction in F_{IO_2} and/or airway pressure within 1 hour) and ≥4 hours from the start of the previous dose.

All data were extracted from the medical records during the first 28 days of age or until death or hospital discharge, whichever occurred first.

Study Outcomes

The primary outcome was endotracheal intubation and liquid surfactant instillation within the first 4 days of age. Gestational age, postnatal age, concurrent medical problems, and risk of respiratory failure are each important modifiers of whether an individual patient requires liquid surfactant therapy. The decision to intubate a newborn with RDS is both highly complex and individualized. During pretrial discussions, site investigators were unanimous that this critical decision be left up to the clinical provider; not only would it add pragmatic strength, but it would be ethically compliant with the infant's best interest. We, therefore, did not set criteria for the primary end point nor require documentation of the clinician's reasoning for making this decision. Secondary outcomes included respiratory support at 3, 7, and 28 days of age or hospital discharge, whichever was earlier. Safety outcomes included any adverse event during aerosol delivery; pneumothorax or other lung air leak; pulmonary hemorrhage; pneumonia (as determined by the clinical team); other severe complications of prematurity (grade 3 or 4 intraventricular hemorrhage, patent ductus arteriosus requiring treatment, hypotension requiring treatment, necrotizing enterocolitis stage ≥2, neutropenia, or sepsis).

Statistical Analysis

Measured outcomes were summarized by using standard descriptive statistics; except where noted differently, values are mean ± SD. Efficacy analyses were planned for each cohort separately. Primary outcome analyses, both intent to treat and as treated, were conducted by using a 1-sided Cochran-Mantel-Haenszel test, stratified by site. Robustness was assessed by using logistic regression, with the additional covariates (gestational age, birth weight, age when randomly assigned, sex, delivery mode, and antenatal steroids). The relative risk (RR) and corresponding 90% confidence interval (CI) were computed for the primary outcome. Group comparisons of secondary variables were performed by using the Cochran-Mantel-Haenszel test or Fisher's exact test, depending on observed frequencies. A nominal significance level of 5% was used.

Study sample size was based on a proposed RR for the primary outcome. We estimated a 60% rate of intubation within the usual care group based on a study of supraglottic surfactant administration in a similar clinical population.[26] A clinically meaningful effect was defined as a 20% relative decrease in the intubation rate. Calculations revealed a sample size of 229 per group (458 total) in cohort 1 would result in >80% power.

RESULTS

Parents of 772 infants were approached for consent. Of these infants, 477 were randomly assigned into the 2 cohorts between April 2017 and June 2018 (Fig 1). Nearly all (96%) were enrolled in cohort 1. Having reached our sample size target for cohort 1, further enrollment in cohort 2 was discontinued. The remainder of this article refers to cohort 1 only.

The demographic characteristics and baseline respiratory supports were similar between the 2 study groups (Table 1). Although not required by study protocol, 322 of 457 infants had a chest radiograph on day 1; in all cases, the radiograph confirmed a diagnosis of RDS (Supplemental Fig 9). There were 230 infants randomly assigned to the aerosol group; 225 received 334 treatments at a median age of 5 hours (interquartile range [IQR]: 3–7); 149 (66%) received only one aerosol treatment, 43 (19%) received 2 treatments, and 33 (15%) received 3 treatments. There was no difference in the number of treatments when stratified by gestational age (2-week blocks) or birth weight (250 g blocks). The mean dose volume was 12.9 ± 4.7 mL, and administration took an average of 68 ± 34 minutes.

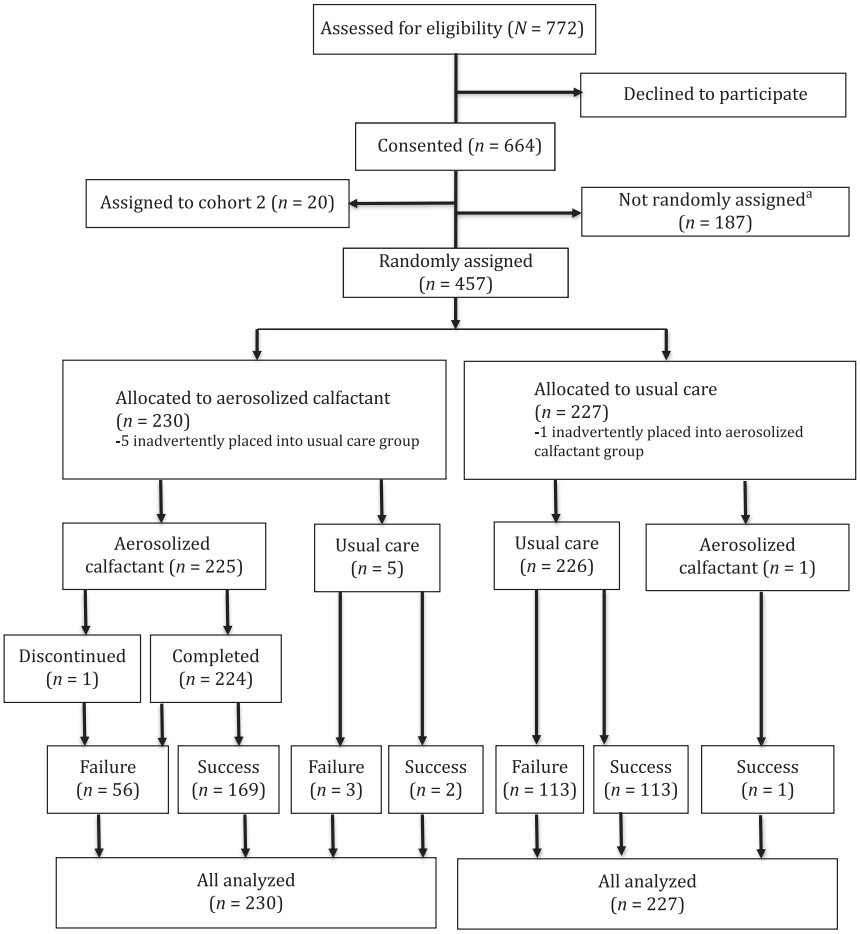

FIGURE 1

CONSORT (Consolidated Standards of Reporting Trials) flow diagram for AERO-02 study. [a] It is presumed that most never met entry criteria; however, some consented patients may have not been randomly assigned for other reasons.

Primary Outcome

Intubation for liquid surfactant instillation occurred in 113 infants (50%) in the usual care group and 59 infants (26%) in the aerosol group, in an intent-to-treat analysis ($P < .0001$); RR: 0.51 (90% CI: 0.41–0.63). The number needed to treat to prevent 1 intubation is 5. Adjustment for gestational age, birth weight, age when randomly assigned, sex, delivery mode, and antenatal steroids did not impact significance ($P < .0001$). Rates of intubation were consistently lower for infants in the aerosolized calfactant group in all 2-week gestational age brackets except the lowest (23–24 weeks), in which all infants required intubation. (Fig 2). Age at first instillation was significantly later in the aerosol group (Table 2). Primary outcome efficacy varied by center but favored aerosolized calfactant in all but 2 centers (Fig 3).

Protocol Violations

There were 14 infants with protocol violations. Six did not receive the assigned treatment; 1 infant randomly assigned to usual care received aerosol, and 5 infants randomly assigned to aerosol received usual care. Six infants exceeded eligibility requirements at randomization; each required F_{IO_2} >0.40 and/or had hypercarbia. One infant did not meet the eligibility criteria; this infant was in room air at randomization. One infant received an incorrect aerosol dose. When infants were reassigned to the group that represented their actual treatment (as treated) and ineligible infants were removed (as treated and eligible), analysis of the primary outcome did not significantly change compared to the intent-to-treat analysis (Table 2).

Secondary Outcomes

There were no differences in respiratory support on days 3, 7, and 28 (discharge) between groups (Supplemental Table 5). The incidence of pulmonary air leaks was similar between groups (Table 3).

Of 334 aerosol treatments, 22 were briefly interrupted, primarily because of surfactant foaming around the pacifier. There were no monitor events (desaturation or bradycardia) during treatment that required intervention. One treatment was discontinued when pink-colored surfactant dribbled from the infant's mouth. This infant had remained stable during treatment, and no lesions were noted in the mouth. In a laboratory investigation by the sponsor, it was determined that 0.1 mL of blood added to 1 mL of calfactant is sufficient to turn the material pink or red; we concluded that a trace amount of residual blood (either maternal or neonatal) in the infant's mouth after birth was the likely cause.

One or more severe complications of prematurity occurred in 17 infants (7%) in the aerosol group and 14 infants (6%) in the usual care group. Chronic lung disease, defined as any respiratory support at 28 days of age, was diagnosed in 46 (20%) infants in the aerosol group and 38 infants (17%) in the usual care group ($P = .38$). There was 1 death in the usual care group due to nonrespiratory causes.

Post Hoc Analyses for Bias

Because the study was unblinded and the primary outcome was dependent on clinical decision-making, we explored for the possibility of treatment bias. Because

TABLE 1 Characteristics of Patients at Random Assignment

Characteristic	Aerosolized Calfactant (n = 230)	Usual Care (n = 227)
Male sex, No. (%)	133 (58)	136 (60)
Gestational age, wk, mean ± SD	33.2 ± 3.2	33.1 ± 3.1
Birth wt, g, mean ± SD	2126 ± 828	2081 ± 769
Singleton births, No. (%)	162 (70)	169 (74)
Vaginal delivery, No. (%)	60 (26)	77 (34)
Antenatal steroids for fetal lung maturation, No. (%)		
None	62 (27)	58 (26)
<12 h before delivery	39 (17)	44 (19)
>12 h before delivery	113 (49)	109 (48)
Unknown	16 (7)	16 (7)
Apgar score, median (IQR)		
1 min	7 (2)	7 (2)
5 min	8 (1)	8 (1)
Respiratory status at random assignment		
F_{IO_2}, mean ± SD	0.30 ± 0.10	0.32 ± 0.14
nCPAP, No. (%)	163 (71)	158 (70)
NIPPV, No. (%)	24 (10)	26 (11)
High-flow nasal cannula, No. (%)	6 (3)	11 (5)
Supplemental oxygen only, No. (%)	20 (9)	15 (7)
Not recorded, No. (%)	16 (7)	17 (7)
Age at random assignment[a], No. (%)		
<4 h	96 (42)	107 (51)
4–8 h	94 (41)	68 (33)
>8 h	40 (17)	33 (16)

NIPPV, noninvasive positive pressure ventilation.

[a] Data are missing for 19 infants in the usual care group; the percentage shown is based on N = 208.

the rate of intubation for liquid surfactant in our usual care group (50%) was lower than expected, there is no suggestion of overtreatment bias regarding the primary outcome in that group. We, therefore, focused on undertreatment bias within the aerosol group. There were 171 infants in that group who were never intubated; 154 of these had received <3 doses. If their condition worsened, we would expect that they would have received all 3 doses of aerosolized calfactant and/or be intubated for liquid surfactant, but neither happened. That leaves 17 infants who received all 3 aerosol doses allowed by protocol but were never intubated; if their condition worsened but they were not intubated, bias is created favoring the aerosol group. However, even if we consider all 17 to have been intubated, the difference in primary outcome rates between the 2 groups would still be significant, 33% vs 50% (RR: 0.66; 95% CI: 0.53–0.83; P = .0003). Additional post hoc analyses are presented in Supplemental Figs 4–7.

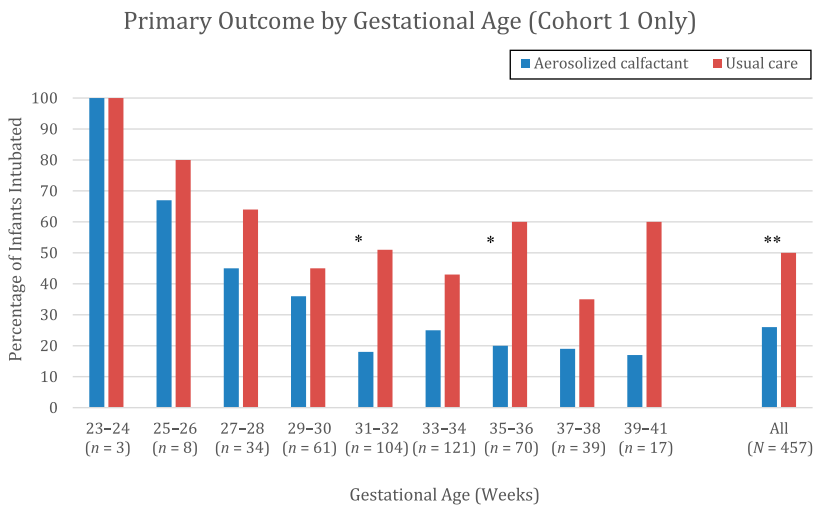

FIGURE 2

Primary outcome (intubation for liquid surfactant) by gestational age. The percentage of infants intubated and treated with liquid surfactant instillation is shown for each study group (right hand) and broken down by 2-week gestational age blocks (left hand). The aerosolized calfactant group is shown in blue, and the usual care group is shown in red. * P <.005; ** P <.0001 by Fisher's exact test.

DISCUSSION

This large, multicenter, RCT in neonates requiring noninvasive respiratory support for suspected or confirmed RDS revealed that aerosolized calfactant reduces the need for intubation and liquid surfactant instillation by nearly 50%. As a result, far fewer infants in the aerosol group were subjected to the potential harms of laryngoscopy and intubation.

To date, clinical trials of aerosolized surfactant administration in newborns with RDS have been small, mostly uncontrolled, and with mixed results. The first was by Robillard et al[27] in 1964, who administered L-α-lecithin by microaerosol to 11 infants ranging from 680 to 3120 g birth weight; 8 infants showed improvement and survived to discharge. In the ensuing 55 years, there have been 6 published studies of aerosolized surfactant.[24,25,28–31] Three of these were prospective, including 1 sequentially assigned pilot study[30] and 2 RCTs[24,25]; in 1 RCT, researchers found a reduction in nCPAP failure rates,[25] whereas, in the other, researchers found no differences.[24]

The efficacy of an aerosolized surfactant is likely dependent on a complex interaction among multiple factors, including the type of

TABLE 2 Primary Efficacy Outcome: Intubation and Liquid Surfactant Instillation

	Intent to Treat		As Treated		As Treated and Eligible[a]	
	Aerosolized Calfactant	Usual Care	Aerosolized Calfactant	Usual Care	Aerosolized Calfactant	Usual Care
Number included	230	227	226	231	219	230
Intubated, No. (%)	59 (26)[b]	113 (50)	56 (25)[b]	116 (50)	52 (24)[b]	115 (50)
Age at first intubation, h, mean ± SD	24 ± 16[c]	10 ± 13	25 ± 16[c]	10 ± 13	26 ± 16[c]	10 ± 13

[a] Excludes 7 patients entered who did not meet the entry criteria and 1 patient in the aerosol group who did not receive the correct aerosol dose.
[b] $P < .001$
[c] $P < .05$, compared to usual care.

surfactant, nebulization method, lung recruitment strategy, age at administration, and RDS severity. Given the progressively worsening nature of lung injury with RDS, we would anticipate that aerosolized surfactant would be more effective earlier in the course of disease. We, therefore, selected infants with mild to moderate respiratory distress and treated them early, at a median age of 5 hours.

Surfactant delivery by aerosol is inefficient, but current clinical dosing may be far greater than needed to treat RDS. In lung-lavaged, spontaneously breathing rabbits, aerosolized surfactant improved lung function at a significantly lower dose than bolus.[32] By using the lung deposition rate from that study (14%), the surfactant dose used in our study would equate to ~29 mg/kg reaching the distal functional lung space, or approximately one-half the amount present in a healthy term infant.

Our study is the first to reveal the efficacy of an aerosolized surfactant delivery system that does not require a respiratory circuit interface. In all previous studies, researchers delivered aerosolized surfactant in-line with nCPAP, with the potential to interfere with respiratory support. By using a separate, pacifier interface, both the aerosol delivery and nCPAP flow can be managed independently, which should allow for safer patient care.

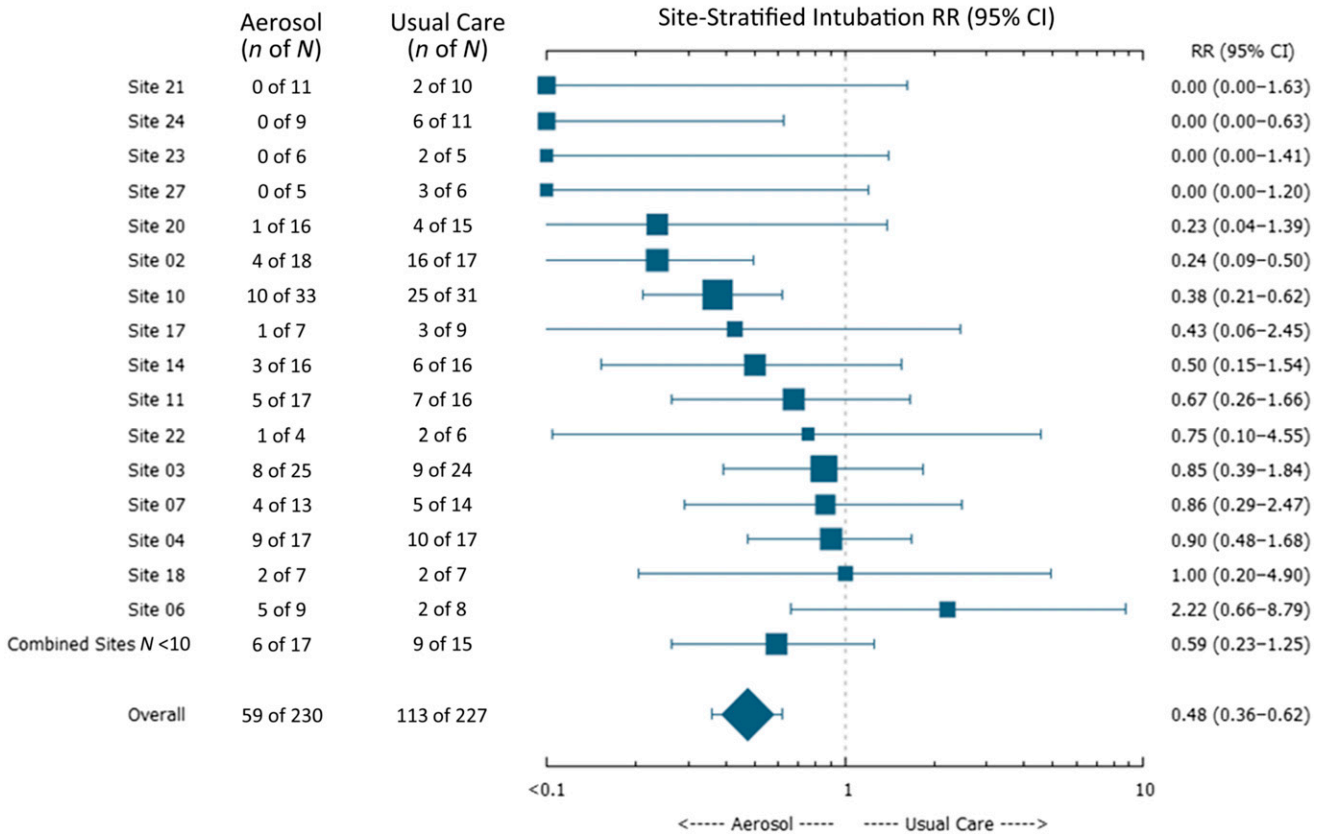

FIGURE 3
Forest plot of primary efficacy outcome by study sites. The primary outcome was intubation and instillation of liquid surfactant. *n* of *N* is the number who experienced this outcome divided by the number randomly assigned. Data are shown for cohort 1 only. The combined sites were the 6 that each enrolled <10 total patients. The RR of the primary outcome, with 95% CIs, is shown in right-hand column.

TABLE 3 Pulmonary Air Leaks During First 72 Hours of Age

Characteristic	Aerosolized Calfactant (n = 230)	Usual Care (n = 227)	P
Any air leak, No. (%)	14 (6.1)	11 (4.8)	.56
Type of air leak, No. (%)[a]			.78[b]
Pneumothorax only	8 (57)	7 (64)	—
Pneumomediastinum only	1 (7)	2 (18)	—
Pulmonary interstitial emphysema only	1 (7)	1 (9)	—
Multiple air leaks	4 (29)	1 (9)	—
Relation to liquid surfactant, No. (%)[a]			.17[b]
Never received liquid surfactant	3 (21)	1 (9)	—
Before receiving liquid surfactant	5 (36)	1 (9)	—
After receiving liquid surfactant	6 (43)	9 (82)	—

—, not applicable.

[a] Percentage of all air leaks (not patients).

[b] P value across all subgroups via Fisher's exact test.

Recognizing that neonatal intubation is difficult and potentially harmful, less invasive methods have been sought; these include the use of an intratracheal catheter (minimally invasive surfactant therapy or less invasive surfactant administration) or a supraglottic device (surfactant administration through laryngeal or supraglottic airways). These methods appear to be safe and effective and may reduce the need for mechanical ventilation,[16–19,33–35] but more studies are needed.[36–38]

Aerosolized surfactant delivery is different from other minimally invasive administration methods. Minimally invasive surfactant therapy and less invasive surfactant administration require laryngoscopy and catheter placement below the vocal cords,[39] whereas surfactant administration through laryngeal or supraglottic airways requires placement of a specialized device into the supraglottic airway; both techniques require a skilled operator. Aerosolized surfactant delivery is unique in that no instrumentation of the airway is needed and no mechanical apparatus is introduced into the airway. Thus, aerosolization may be the gentlest, easiest, and least invasive approach.[23]

Our randomized, controlled study has several strengths, including a large sample size, wide range of gestational ages, and multicenter nature. We also believe that our pragmatic approach adds an important practical aspect. In this study, we enrolled relatively few infants <28 weeks' gestation; many were ineligible because of intubation in the delivery room or having more severe respiratory distress. Sicker, more premature infants will more likely fail noninvasive respiratory support and require early surfactant treatment.[40] Because a dose of aerosolized calfactant takes 1 to 2 hours to administer, we did not want to delay definitive treatment; this is consistent with the pragmatic nature of our study and best clinical practice. Our results suggest that aerosolized calfactant may have delayed intubation and liquid surfactant instillation in some infants who ultimately needed this intervention, but this did not adversely affect their respiratory outcomes.

The study was not blinded. A nontherapeutic sham procedure such as aerosolization of saline for the usual care group was deemed ethically unacceptable because it could complicate respiratory therapy with no benefit. Masking, by using a second team of care providers, was considered impractical; a recent pilot study of aerosolized surfactant had to be halted because of the financial burden imposed in part by such a design.[25] More importantly, during a pretrial pilot study, an immediate positive clinical effect was noted in virtually all treated infants; masking would, therefore, be ineffective. Proper masking would also require separating parents from their newborn for 2 to 3 hours each time an aerosol treatment was given; we deemed that unacceptable from a family-centered perspective.

Chest radiographs were not required by study protocol, consistent with our pragmatic design and to minimize radiation exposure. Without radiographic confirmation, it is possible that some infants may have had etiologies other than RDS for their respiratory distress, such as transient tachypnea. However, >70% of infants had an early chest radiograph, and, in every case, their radiograph was consistent with RDS.

The unblinded intervention and lack of prespecified criteria for the primary outcome introduce the potential for treatment bias; however, post hoc analysis suggests that our primary outcome findings would remain significant in the event that treatment bias was present.

CONCLUSIONS

Aerosolized calfactant can be readily administered to newborn infants with mild to moderate respiratory distress and reduces the need for intubation and liquid surfactant instillation during the first 4 days of age. The use of aerosolized calfactant avoids the risks associated with endotracheal intubation and expands opportunities for surfactant therapy in the hospitalized patient.

ABBREVIATIONS

CI: confidence interval
Fio_2: fraction of inspired oxygen concentration
IQR: interquartile range
nCPAP: nasal continuous positive airway pressure
RCT: randomized controlled trial
RDS: respiratory distress syndrome
RR: relative risk

Dr Cummings helped design the study, conducted initial data analyses, and created, reviewed, and revised all manuscript drafts including the final version; Drs Wilding and Egan conceptualized and designed the study (including data collection instruments), conducted data analyses, coordinated and supervised data collection, and worked on the drafts of the manuscript (including writing, table, and figure preparation and critical review of each draft version); Drs Gerday, Minton, Katheria, Albert, Flores-Torres, Famuyide, Lampland, Guthrie, Kuehn, Weitkamp, Fort, Abu Jawdeh, Ryan, Martin, Swanson, Mulrooney, Eyal, Gerstmann, and Kumar contributed to the acquisition of data and worked on the drafts of the manuscript (including writing, table, and figure preparation and critical review of each draft version); and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Deidentified individual participant data that underlie the results reported in this article will be made available, in addition to study protocols, informed consent, and statistical analysis plan. The data will be available beginning 3 months and ending 5 years after article publication to investigators whose proposed use of the data has been approved by an independent review committee identified for this purpose. Proposals should be directed to cummings.AMBI@gmail.com. To gain access, data requestors will need to sign a data access agreement.

A complete list of Aero-02 investigators, along with affiliations, can be found in the Supplemental Information.

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POTENTIAL CONFLICT OF INTEREST: Drs Cummings and Wilding are contracted consultants to ONY Biotech. Dr Egan is chief medical officer of ONY Biotech; the other authors have indicated they have no financial relationships relevant to this article to disclose.

COMPANION PAPER: A companion to this article can be found online at www.pediatrics.org/cgi/doi/10.1542/peds.2020-021576.

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