The Randomized, Controlled Trial of Late Surfactant: Effects on Respiratory Outcomes at 1-Year Corrected Age

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Objective To determine the effects of late surfactant on respiratory outcomes determined at 1-year corrected age in the Trial of Late Surfactant (TOLSURF), which randomized newborns of extremely low gestational age (≤28 weeks' gestational age) ventilated at 7-14 days to late surfactant and inhaled nitric oxide vs inhaled nitric oxide-alone (control).

Study design Caregivers were surveyed in a double-blinded manner at 3, 6, 9, and 12 months' corrected age to collect information on respiratory resource use (infant medication use, home support, and hospitalization). Infants were classified for composite outcomes of pulmonary morbidity (no PM, determined in infants with no reported respiratory resource use) and persistent PM (determined in infants with any resource use in ≥3 surveys).

Results Infants (n = 450, late surfactant n = 217, control n = 233) were 25.3 ± 1.2 weeks' gestation and 713 ± 164 g at birth. In the late surfactant group, fewer infants received home respiratory support than in the control group (35.8% vs 52.9%, relative benefit [RB] 1.28 [95% CI 1.07-1.55]). There was no benefit of late surfactant for No PM vs PM (RB 1.27; 95% CI 0.89-1.81) or no persistent PM vs persistent PM (RB 1.01; 95% CI 0.87-1.17). After adjustment for imbalances in baseline characteristics, relative benefit of late surfactant treatment increased: RB 1.40 (95% CI 0.89-1.80) for no PM and RB 1.24 (95% CI 1.08-1.42) for no persistent PM.

Conclusion Treatment of newborns of extremely low gestational age with late surfactant in combination with inhaled nitric oxide decreased use of home respiratory support and may decrease persistent pulmonary morbidity. *(J Pediatr 2017;183:19-25).*

Trial registration ClinicalTrials.gov: NCT01022580

Extreme prematurity carries a risk of ongoing pulmonary morbidity (PM) and resource use following hospital discharge.[1-4] Interventional trials of both drugs and respiratory support strategies in extremely low gestational age newborns (ELGANs) focus on decreasing the rate of bronchopulmonary dysplasia (BPD) at 36 weeks' postmenstrual age (PMA).[5-8] Although BPD is an imperfect

BD	Bronchodilator
BPD	Bronchopulmonary dysplasia
ELGAN	Extremely low gestational age newborn
GA	Gestational age
ICS	Inhaled corticosteroids
iNO	Inhaled nitric oxide
NO CLD	Inhaled Nitric Oxide to Prevent Chronic Lung Disease
PM	Pulmonary morbidity
PMA	Postmenstrual age
RB	Relative benefit
TOLSURF	Trial of Late Surfactant

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predictor of later PM,[1,4,9] clinical trials have not reported broadly accepted later respiratory outcomes. Outcomes previously evaluated at 1-2 years of age include respiratory symptoms, medication use, respiratory exacerbations, and hospitalizations due to respiratory disease.[2-4,10-12]

The Trial of Late Surfactant (TOLSURF) was a randomized, controlled, masked clinical trial in which ELGANs at high risk for BPD who remained intubated in the second week of life were randomized to late surfactant (up to 5 doses) and inhaled nitric oxide (iNO) vs iNO alone.[13] We found no difference in the primary outcome of survival without BPD at 36 weeks' PMA. A potential benefit of treatment with late surfactant, however, emerged with a later respiratory assessment at 40 weeks' PMA (term). Data on respiratory resource use after hospital discharge were collected. We sought to determine whether there were effects of late surfactant on several clinically relevant respiratory outcomes determined through 1-year corrected age. We hypothesized that late surfactant and iNO would improve respiratory outcomes compared with iNO alone.

Methods

The TOLSURF study (ClinicalTrials.gov: NCT01022580) has been described in detail.[13] Parental informed consent for participation was obtained under institutional review board approval at 25 US hospitals. In brief, 511 infants ≤ 28 0/7 weeks' gestational age (GA) underwent stratified randomization (<26 weeks' GA or ≥ 26 weeks' GA) by site to late surfactant and iNO vs iNO alone at 7-14 days (n = 252 and 259, respectively). Calfactant (Infasurf; ONY Inc, Amherst, New York) was administered in standard doses every 1-3 days for up to 5 doses in the late surfactant group. Control (iNO alone) infants had no intervention (sham procedure behind a screen to maintain blinding). All infants received iNO for a 25-day course, per the protocol of our previous study of Nitric Oxide to Prevent Chronic Lung Disease (NO CLD).[14,15] The primary outcome of TOLSURF was survival without BPD, determined by oxygen/flow reduction challenge at 36.0 ± 1 weeks' PMA. Infants on nasal cannula support with effective fraction of inspired oxygen < 0.30 who remained hospitalized at 40 weeks' PMA had a repeat assessment. No statistically significant differences were identified in primary or secondary outcomes during the neonatal hospitalization.[13] Clinical study personnel and families remained blinded to treatment group assignment through the follow-up period (completed February 2016). Unblinded outcomes were reviewed periodically by a data safety monitoring board appointed by the National Institutes of Health.

Parents/caregivers were surveyed at 3, 6, 9, and 12 months' corrected age (for prematurity) for interval events since discharge or last contact. Responses to questions regarding respiratory medication prescription, hospitalization for respiratory illness, and home respiratory support (supplemental oxygen by nasal cannula or tracheostomy with or without assisted ventilation/oxygen) were collated. Specific respiratory medication categories queried were inhaled bronchodilators (BD), inhaled corticosteroids (ICS), diuretics, systemic steroids, and pulmonary vasodilators. We also asked caregivers if they had been told by a medical professional that their child had wheeze on auscultation. These questions were posed over the same time interval, since the last contact.

Respiratory Outcomes at 1-Year Corrected Age

We focused the analysis of PM following neonatal discharge on caregiver-reported health resource use for respiratory indications in 3 domains (medications, hospitalization, and home support) using a short recall interval. We predetermined several outcomes to quantify the degree and type of morbidity experienced by these infants. Our primary outcomes were PM and persistent PM. We assigned an outcome of no PM to infants whose caregivers reported no medications, hospitalizations, or home respiratory support on any survey through 12 months' corrected age. We assigned an outcome of any PM to all other infants. We defined persistent PM in infants with morbidity on any domain on at least 3 surveys. Infants with morbidity on 2 or fewer surveys were classified as no persistent PM.

A committee of investigators who remained blinded to treatment assignment evaluated 37 infants with incomplete survey data who were unclassified for one or both outcomes, for adjudication of missing outcomes. Using simple imputation when data were missing between 2 other time points (eg, no resource use reported), and additional respiratory resource use data collected during follow-up visits in the second year of life and among infants with prolonged neonatal hospitalizations beyond 3 months' corrected age, we were able to impute either missing PM or persistent PM for 8 infants, and both for 1 infant. Four infants had no follow-up data, 2 had insufficient data for both outcomes (but contributed other data on resource use), and the remainder were unable to be classified for one missing outcome (**Figure 1**; available at www.jpeds.com). Infants were classified as a wheezing phenotype if caregivers reported any ICS or BD use or wheeze (vs no wheezing phenotype). They were subclassified into 4 ordered categories of wheezing phenotype: likely (ICS with/without BD use), probable (BD use with/without wheeze), possible (wheeze without BD/ICS use), or none (no ICS, BD, or wheeze).

Statistical Analyses

To estimate treatment effect, we used generalized estimating equations to account for clustering of siblings. Analyses of baseline characteristics and potential modifiers of infant lung disease did not account for clustering. All analyses were by intent-to-treat, based on initial randomized allocation. Because of the known impact of sociodemographic factors in postdischarge outcomes among infants born extremely preterm, we planned a priori to adjust estimations of treatment effect for our primary outcomes (PM and persistent PM) for differences ($P < .05$) in baseline characteristics noted between groups.

Results

Patients were enrolled between January 2010 and September 2013. Of 471 infants alive at 36 weeks' PMA, 455 who remained in the study were discharged alive and 5 infants died