Randomized Trial of Late Surfactant Treatment in Ventilated Preterm Infants Receiving Inhaled Nitric Oxide

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Objective To assess whether late surfactant treatment in extremely low gestational age (GA) newborn infants requiring ventilation at 7-14 days, who often have surfactant deficiency and dysfunction, safely improves survival without bronchopulmonary dysplasia (BPD).

Study design Extremely low GA newborn infants (GA ≤28 0/7 weeks) who required mechanical ventilation at 7-14 days were enrolled in a randomized, masked controlled trial at 25 US centers. All infants received inhaled nitric oxide and either surfactant (calfactant/Infasurf) or sham instillation every 1-3 days to a maximum of 5 doses while intubated. The primary outcome was survival at 36 weeks postmenstrual age (PMA) without BPD, as evaluated by physiological oxygen/flow reduction.

Results A total of 511 infants were enrolled between January 2010 and September 2013. There were no differences between the treated and control groups in mean birth weight (701 ± 164 g), GA (25.2 ± 1.2 weeks), percentage born at GA <26 weeks (70.6%), race, sex, severity of lung disease at enrollment, or comorbidities of prematurity. Survival without BPD did not differ between the treated and control groups at 36 weeks PMA (31.3% vs 31.7%; relative benefit, 0.98; 95% CI, 0.75-1.28; $P = .89$) or 40 weeks PMA (58.7% vs 54.1%; relative benefit, 1.08; 95% CI, 0.92-1.27; $P = .33$). There were no between-group differences in serious adverse events, comorbidities of prematurity, or severity of lung disease to 36 weeks.

Conclusion Late treatment with up to 5 doses of surfactant in ventilated premature infants receiving inhaled nitric oxide was well tolerated, but did not improve survival without BPD at 36 or 40 weeks. Pulmonary and neurodevelopmental assessments are ongoing. *(J Pediatr 2016;168:23-9)*.

Trial registration ClinicalTrials.gov: NCT01022580.

Bronchopulmonary dysplasia (BPD), initially described by Northway in 1967,[1] is the most common form of chronic lung disease in children, with an estimated 15 000 new cases annually in the US. This condition affects infants born prematurely, is a major contributor to the $22 billion cost of prematurity each year, and is associated with long-term pulmonary disability, neurodevelopmental abnormalities, and death.[2-4] With increased survival of extremely low gestational age newborn (ELGAN) infants, defined as infants born at ≤28 weeks gestational age (GA), another form of BPD has emerged,

AE	Adverse event	NCPAP	Nasal continuous positive airway pressure
BPD	Bronchopulmonary dysplasia		
DSMB	Data Safety Monitoring Board	NIH	National Institutes of Health
ELGAN	Extremely low gestational age newborn	NO CLD	Inhaled Nitric Oxide to Prevent Chronic Lung Disease
FiO_2	Fraction of inspired oxygen	PMA	Postmenstrual age
GA	Gestational age	SAE	Serious adverse event
iNO	Inhaled nitric oxide	SP-B	Surfactant protein B
IVH	Intraventricular hemorrhage	TA	Tracheal aspirate
		TOLSURF	Trial of Late Surfactant

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characterized by impaired alveolar and microvascular development with excess tone and reactivity of airway smooth muscle.[5-10]

Despite antenatal glucocorticoid treatment to enhance lung maturation and replacement surfactant treatment at birth, as well as the more aggressive use of nasal continuous positive airway pressure (NCPAP) and nasal intermittent positive pressure ventilation, premature infants often need prolonged intubation and mechanical ventilation support and/or supplemental oxygen. BPD occurs in >70% of surviving ELGAN infants who require mechanical ventilation support beyond 7 days of age.[11,12] Factors contributing to BPD include structurally immature lungs, a compliant chest wall, deficiency and dysfunction of pulmonary surfactant, oxidant stress, immature respiratory drive, perturbed intrauterine environment, exposure to infection and inflammation, and genetic susceptibility.

Most of these infants experience clinical episodes of increased need for ventilatory support associated with dysfunctional surfactant, primarily low surfactant protein B (SP-B).[13] We and others have reported results from small studies of late surfactant treatment in premature infants who required ventilatory support beyond 1 week of life.[14-19] Surfactant treatment was well tolerated, with short-term improvement in Respiratory Severity Score, calculated as mean airway pressure × fraction of inspired oxygen (FiO_2), and SP-B content.[18,19] However, in these pilot studies of late surfactant alone, there was no improvement in survival without BPD at 36 weeks.

These observations provided the rationale for a large clinical trial of later doses of surfactant (Trial of Late Surfactant [TOLSURF]) to prevent episodes of respiratory decompensation and BPD. In our previous study (Inhaled Nitric Oxide to Prevent Chronic Lung Disease [NO CLD]), a 25-day course of inhaled nitric oxide (iNO) at 20 ppm started between 7 and 14 days of age significantly improved survival without BPD at 36 and 40 weeks, as well as respiratory status to age 1 year.[11,20,21] iNO did not improve long-term surfactant function[22] or markers of pulmonary inflammation and oxidative stress.[23,24] For this multifactorial disorder, it is likely that a combination of treatments directed at different aspects of the pathogenesis will be needed to improve outcomes. To address this question, we conducted a randomized trial of late surfactant vs placebo sham procedure in premature infants receiving iNO therapy.

Methods

TOLSURF was a masked, randomized, sham-controlled trial conducted in 25 US hospitals (ClinicalTrials.gov: NCT01022580). The study was designed to assess the effect of late doses of surfactant on BPD at 36 weeks postmenstrual age (PMA) in ELGAN infants who required intubation and mechanical ventilation between 7 and 14 days of age and were receiving iNO. Infants who had a life-threatening congenital abnormality, were clinically unstable, had bilateral grade 4 intraventricular hemorrhage (IVH), or were unlikely to be available for long-term pulmonary and neurodevelopmental follow-up were excluded.

The trial was conducted under the regulatory oversight of the Food and Drug Administration (IND #79 367 for the combined use of calfactant with iNO is held by the principal investigator, Roberta Ballard, MD. The research protocol was approved by the Institutional Review Boards of the participating institutions, and a parent of each infant provided written informed consent. The consent included "opt-in/opt-out" permission for long-term banking of biospecimens and DNA. The consent was revised and reapproved by the Data Safety Monitoring Board (DSMB) and the Institutional Review Boards after the National Institutes of Health (NIH) Consensus Conference on the use of iNO in preterm infants.[25] The National Heart, Lung, and Blood Institute–appointed DSMB approved the protocol, informally reviewed safety data after enrollment of every 60-80 infants, and conducted 2 interim efficacy/futility analyses when both 36- and 40-week fully cleaned outcome data were available on 25% and 50% of the recruitment expectation of 524 subjects. The second futility analysis (conducted with complete outcome data for 301 infants [57% of 524]) was presented to the DSMB in August 2013. At that time, the DSMB recommended to the National Heart, Lung, and Blood Institute that the study be terminated, stating that "based on a determination that the study treatment is very unlikely to demonstrate efficacy, the DSMB decided that continuation of study treatment intervention could no longer be justified." At the time of termination, although 511 of the planned 524 infants had been randomized, complete cleaned outcome data to 40 weeks were not yet available for more than 200 infants.

For this trial, we selected calfactant (Infasurf; ONY Inc, Amherst, New York), a natural surfactant extracted from bovine lung lavage fluid, which has consistent amounts of SP-B (0.9% phospholipid) and surfactant protein C (1.5% phospholipid). Standard clinical doses of calfactant were administered to treated infants (the late surfactant group) by research staff behind a screen if the infant remained intubated (up to maximum of 5 doses). Control infants received a sham procedure (no intervention) behind the screen. Monitor and ventilator alarms were turned off during dosing to avoid unblinding of clinical staff. To accommodate research staff availability and infant instability, the dosing interval was not strict but could be repeated every 24-72 hours, up to 5 doses if the infant still required intubation. Dosing could be discontinued by physician request or parental withdrawal from the study. Clinical guidelines (**Appendix 2**; available at www.jpeds.com) for management of ventilation, including reintubation, blood pressure management, and use of caffeine and postnatal corticosteroids, were developed, presented at each clinical site, and approved by investigators.

All treated infants received iNO (Ikaria, Hampton, New Jersey) according to the protocol followed in the NO CLD trial.[11,20] Although iNO therapy was accepted practice in the units participating in the trial, there was a concern about the potential cost for families in light of the NIH Consensus