Pulmonary Function at Hospital Discharge in Preterm Infants Randomized to a Single Rescue Course of Antenatal Steroids

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Objective To compare the pulmonary function, measured at birth and at hospital discharge, of infants whose mothers had been randomized to a single rescue course of antenatal steroids versus those whose mothers had been randomized to placebo.

Study design This study involved follow-up at hospital discharge of subjects of a randomized, double-blinded trial. In the original trial, pregnant women at ≥14 days after their initial course of antenatal steroids and <34 weeks' gestation were randomized to rescue antenatal steroids (44 mothers, 56 infants) or placebo (41 mothers, 57 infants). Passive respiratory compliance (Crs), passive respiratory resistance, and functional residual capacity were measured in all infants at birth and again at discharge to evaluate changes in pulmonary mechanics over time. Statistical analyses were based on intention to treat.

Results We previously reported that compared with infants in the placebo group, infants in the rescue antenatal steroids group had a higher mean Crs value measured within 72 hours of birth (1.21 vs 1.01 mL/cm H_2O/kg; $P < .05$). Here we show that the Crs benefit in the antenatal steroids group was sustained until discharge. Infants in the placebo group demonstrated improvement in Crs such that by discharge, there was no difference in mean Crs between the rescue antenatal steroids and placebo groups (1.18 vs 1.22 mL/cm H_2O/kg).

Conclusions Rescue antenatal steroids significantly increased Crs measured within 72 hours of birth, and this increase was sustained until hospital discharge. Preterm infants in the placebo group demonstrated a decreased initial Crs compared with the rescue antenatal steroids group, but achieved a comparable Crs by the time of discharge. *(J Pediatr 2017;181:62-6).*

Trial registration ClinicalTrials.gov: NCT00669383.

Preterm infants exhibit respiratory morbidities as a result of architectural and functional immaturities of the lung. Previous meta-analyses have definitively shown that a single course of antenatal steroids administered before preterm delivery at ≤34 weeks' gestation improves a host of neonatal outcomes.[1] These benefits are evident in both pulmonary function, with improved functional residual capacity (FRC) and passive respiratory compliance (Crs),[2] and clinical outcomes, with reduced rates of neonatal death, respiratory distress syndrome (RDS), intraventricular hemorrhage, and necrotizing enterocolitis, along with decreased durations of mechanical ventilation and oxygen therapy.[1] Given these clear benefits, treatment of women at risk for preterm delivery at ≤34 weeks' gestation with a single course of antenatal steroids remains the standard of care.[3]

Complicating matters, however, is the fact that the beneficial effects of antenatal steroids are time-limited. The improvements in Crs and FRC are clearest in infants born 1-7 days after the first maternal antenatal steroid dose, and wane thereafter.[4] Ideally, all preterm infants would be delivered within this short window of maximal benefit, but accurately predicting the timing of preterm deliveries is difficult. As a result, some women treated with an initial course of antenatal steroids remain undelivered beyond this window of maximal benefit, but remain at risk for preterm delivery. The safety and efficacy of repeated courses of antenatal steroids remains an area of active investigation.

We recently reported that a single rescue course of antenatal steroids significantly increases the initial Crs and decreases the need for oxygen in treated preterm infants compared with controls.[5] In a concurrent similarly designed blinded study of 437 randomized patients, Garite et al reported improvement in a composite neonatal outcome (including RDS, oxygen requirement at 30 days, grade III-IV intraventricular hemorrhage, culture-proven sepsis, periventricular leukomalacia, necrotizing enterocolitis, and perinatal death) without short-term risk.[6] These studies provide evidence that rescue antenatal steroids can

Crs	Passive respiratory compliance
FiO_2	Fraction of inspired oxygen
FRC	Functional residual capacity
PFT	Pulmonary function test
RDS	Respiratory distress syndrome
Rrs	Passive respiratory resistance

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Supported by National Center for Advancing Translational Sciences/National Institutes of Health (NIH; UL1TR000128), NIH/National Heart Lung Blood Institute (K23 HL080231 and R01 HL105447), Office of Dietary Supplement, and American Lung Association (to C.M.). The authors declare no conflicts of interest.

http://dx.doi.org10.1016/j.jpeds.2016.10.022

significantly improve initial pulmonary mechanics and short-term neonatal outcomes. Concerns remain about the potential negative effects on pulmonary function and lung growth after rescue antenatal steroids and the resultant effect on the trajectory of infant pulmonary function. A growing body of evidence demonstrates that lung function tracks along trajectories that are established in early childhood, and that these early trajectories are predictive of lung performance in early adulthood,[7,8] but little is known about the early lung trajectories of infants born prematurely.[9] The objective of the present study was to compare the pulmonary function at birth and discharge of preterm infants randomized to a rescue course of antenatal steroids versus placebo. Because antenatal steroids have been shown to have the physiological effect of inducing surfactant production in the lung before a preterm delivery,[4] we hypothesized that the infants in the rescue antenatal steroids group would maintain a stable Crs level through discharge, and the Crs of the placebo-treated infants would increase during hospitalization to the point where there would be no difference in Crs between the 2 groups at discharge.

Methods

This study is an extension of a previously published prospective, randomized, placebo-controlled study of the impact of rescue antenatal steroids on pulmonary mechanics measured after delivery (ClinicalTrials.gov: NCT00669383).[5] In brief, the study was conducted at the neonatal intensive care units at Oregon Health & Science University (Portland, Oregon) and Sacred Heart Hospital (Pensacola, Florida). Randomization was stratified by gestational age at rescue antenatal steroid dosing (≤28 vs >28 weeks' gestation) and by multiple gestation (twins vs singletons). The study was approved by the Institutional Review Boards at each institution, and informed consent was obtained for each enrolled patient.

Pregnant women were recruited who met the following inclusion criteria: gestation between 26 and <34 weeks at the time of enrollment, ongoing risk of threatened preterm delivery as determined by a care provider, ≥14 days after receipt of an initial course of antenatal steroids, and provision of informed consent. Exclusion criteria included multiple gestation greater than twins, chorioamnionitis, insulin-dependent diabetes mellitus, major chromosomal or fetal abnormality, chronic steroid use during pregnancy, and an initial course of antenatal steroids administered at <24 weeks' gestation.

Women enrolled in the study were randomized to the rescue antenatal steroids arm (given two 12 mg intramuscular injections of betamethasone [Celestone Soluspan; Shering-Plough, Kenilworth, New Jersey]) or the placebo arm (given two 25 mg intramuscular injections of cortisone acetate, an inactive steroid indistinguishable in appearance from betamethasone) at 24-hour intervals.

Within 72 hours of birth, pulmonary function tests (PFTs) were performed to measure Crs, FRC, and Rrs (passive respiratory resistance). These measurements were repeated just before hospital discharge, usually at 34-36 weeks postmenstrual age.

All pulmonary function measurements were obtained using a computerized infant pulmonary function cart (SensorMedics 2600; Sensor-Medics, Yorba Linda, California) via mask or endotracheal tube. Tests were done with the infant supine and quietly asleep and were performed within 72 hours of birth (and before surfactant delivery, if required) and again near the time of discharge. Crs and Rrs were measured using the single-breath occlusion technique to induce the Hering-Breuer reflex, as described previously.[2,4,10,11] Acceptable measurements required a stable end-expiratory baseline, plateau pressure >100 ms and varying by <0.125 cm H_2O, appropriate flow-volume loops by visual inspection, and at least 10 breaths with a measured coefficient of variation <20% in accordance with standard international guidelines.[12-14]

FRC was measured using the nitrogen washout technique.[2,15,16] After creating a calibration curve for each patient, the fraction of inspired oxygen (FiO_2) was increased from baseline to 100% at end expiration. The curve was then used to correlate the nitrogen washout to the infant's FRC. The FRC accounts for dead space and is corrected for temperature, pressure, humidity, and the infant's weight. Acceptable measurements were obtained on a quietly sleeping, supine infant with testing initiated at end expiration, had no evidence of leak on tracing of the washout, and demonstrated consistency, with a coefficient of variation of <10% on at least 3 measurements.

Anthropometric measurements (weight, head circumference, and length) obtained at birth and at hospital discharge were compared in the 2 groups, and corresponding *z*-scores for these measurements were calculated.[17] Clinical variables, including surfactant administration, diagnosis of RDS (defined as clinical signs of respiratory distress with radiographic appearance and the need for supplemental oxygen with an FiO_2 >0.21), respiratory distress with FiO_2 requirement ≥0.30 or ≥0.40 at 24 hours of age, days on mechanical ventilation, and days on supplemental oxygen, were compared as well.

Statistical Analyses

Our analysis was performed on an intention-to-treat basis. For continuous variables, means were compared using the independent-samples Student *t* test. For categorical variables, the 2 groups were compared using the χ^2 test and the Fisher exact test, as appropriate. *P* values and 95% CIs for the primary outcomes were determined using linear mixed modeling to account for the nonindependence of covariates among twins and also to account for additional confounders.[18] This analysis was performed using the same model, which adjusts for covariates including gestational age at birth, twin gestation, maternal smoking, rupture of membranes, and gestational diabetes, applied in a previous study of data from this dataset.[5] Analyses were performed using SPSS for Windows version 21 (IBM, Armonk, New York) and SAS 9.1.3 (SAS Institute, Cary, North Carolina).

Results

As reported previously, patients were recruited from June 2001 through May 2007. Of the 135 women approached to