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Pulmonary Function and Outcomes in Infants Randomized to a Rescue Course of Antenatal Steroids

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SUMMARY

Background/Objective—Our objective was to obtain follow-up pulmonary function testing and assessment of clinical respiratory outcomes, at 1–2 years, in preterm infants whose mothers were randomized to a single rescue course of antenatal steroids (AS) versus placebo.

Methods—Follow-up of a randomized, double-blinded trial. In the original trial pregnant women 14 days after initial course of AS were randomized to rescue AS or placebo. Pulmonary function testing and a standardized respiratory

Results—96 (87%) of available survivors were administered a respiratory questionnaire. Seventy-seven percent of available patients had pulmonary function testing performed. There was no significant difference between groups in incidence of wheezing, asthma, questionnaire were obtained at 1–2 years of corrected age. Respiratory compliance (Crs) was measured with the single-breath occlusion and functional residual capacity (FRC) with the nitrogen washout method. Analysis was by intention-to-treat. respiratory syncytial virus infection, respiratory readmissions, use of bronchodilators or other medications, or in measurements of pulmonary function. There was also no significant difference in corrected age at study, race, gender, or length at the time of pulmonary function testing. Infants in the rescue group had a comparable mean FRC (249.4 mL versus 246.2 mL; adjusted 95% CI for difference –15.45, 38.20; $p=0.37$) versus placebo. There were no differences in tidal volume or Crs.

Conclusion—A rescue course of AS significantly increases Crs within 72 hours of age and decreases oxygen need in newborn infants, without an adverse impact on pulmonary function or clinical respiratory outcomes at 1–2 years of age. [NCT00669383].

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Keywords

Betamethasone; clinical respiratory outcomes; infant pulmonary function; functional residual capacity; rescue antenatal corticosteroids; respiratory compliance; tidal volume

INTRODUCTION

A single course of antenatal steroids (AS) is the standard of care for women at risk for preterm delivery between 24 and 34 weeks of gestation, and significantly decreases mortality and respiratory distress syndrome (RDS).^{1,2} The optimal response occurs if it is given at least 24 hours before but within 7 days of delivery,^{1,2} but this is often difficult to time. The efficacy and safety of repeat courses of AS remains a topic of debate.^{3–8}

Randomized data show weekly courses of AS in preterm infants may improve lung function outcomes.^{4,5} A meta-analysis comparing a single to repeat courses of AS showed repeat courses decreased the occurrence and severity of neonatal lung disease, but in some trials there was a reduction in mean birth weight.⁹ Therefore concern remains of possible harm after repeat AS therapy, particularly in terms of reduced growth (including lung growth) and long-term neurodevelopmental outcome.¹⁰ Growth retardation and changes in lung structure have been shown in animal models after high dose AS therapy.^{11,12} We reported a single rescue course of AS versus placebo (given to pregnant women who remained pregnant 14 days after an initial course of AS) significantly increases respiratory compliance measured within 72 hours of age and decreases oxygen need in their newborns.¹³ These results provide a physiologic basis to the findings of a multicenter trial (n = 558 newborns) documenting significantly decreased composite morbidity and RDS without apparent increased short-term risk, in newborns of pregnant women randomized to a rescue course of AS versus placebo.¹⁴ Although several large trials of weekly/repeat AS therapy have reported their growth and neurodevelopmental follow-up data,^{7–9} there are insufficient data on the relative risks and benefits of a single rescue course of AS. Further, the effects of a rescue course of AS on pulmonary function and clinical respiratory outcomes in infants at 1–2 years of corrected age have not been evaluated.

The objective of the present study was to obtain follow-up pulmonary function testing and clinical respiratory outcomes, at 1–2 years of corrected age, in the original cohort of infants whose mothers were randomized to a single rescue course of AS versus placebo. We hypothesized those infants whose mothers received a rescue course of AS would have comparable pulmonary function and clinical respiratory outcomes to those whose mothers received placebo.

METHODS

Eligibility Criteria

Inclusion criteria for the original randomized, placebo-controlled trial have been previously described.¹³ Briefly, pregnant women 26 to < 34 weeks' gestation, undelivered 14 days after their first course of AS, and at risk of preterm delivery were randomized to a single rescue course of AS versus placebo. Exclusion criteria included: greater than twin

gestations, insulin dependent diabetes, clinical chorioamnionitis, fetal or chromosomal abnormalities, first course of AS at < 24 weeks' gestation, chronic steroid use during pregnancy. The study was conducted at the Neonatal Intensive Care Unit at Oregon Health & Science University (OHSU) (Portland, Oregon) and at Sacred Heart Hospital (Pensacola, Florida). Randomization was stratified by gestational age at dosing (≤ 28 versus > 28 weeks' gestation) and by multiple gestation. The study was approved by the respective Institutional Review Boards and informed consent obtained for each enrolled patient. This study is registered with clinicaltrials.gov [registration number NCT00669383]. Follow-up consisted of assessment of clinical respiratory outcomes and pulmonary function testing. All available survivors were eligible for follow-up at 1–2 years of corrected age with a standardized respiratory questionnaire administered to the parents / primary care takers. Survivors living within the Portland, Oregon area were eligible for follow-up pulmonary function testing as equipment was not available in Pensacola, Florida.

Study Design

This is the respiratory follow-up of a randomized, double-blinded, placebo-controlled trial. Pregnant women assigned to the “rescue AS” group received a course of AS (two 12 mg intramuscular injections of betamethasone [Celestone Soluspan, Schering-Plough Corporation, Kenilworth, NJ] 24 hours apart). Patients assigned to the “placebo” group received 2 doses of placebo that were identical in appearance to the betamethasone.¹³ Group assignment was done using a randomization table. A staff pharmacist performed randomization and study drug preparation at each institution, and all patients, investigators and care providers were unaware of treatment allocation. The primary outcome was to compare pulmonary function within 72 hours of birth between groups. Secondary outcomes included comparison of follow-up pulmonary function testing and assessment of clinical respiratory outcomes between groups, at 1–2 years of corrected age. All outcomes were assessed blinded to treatment group allocation.

Measurements

For assessment of clinical respiratory outcomes, medical history and a standardized respiratory questionnaire¹⁵ were obtained from the parents/ primary care takers of all available survivors at 1–2 years of corrected age. Clinical respiratory outcomes included: incidence of wheezing, physician-diagnosed asthma, respiratory syncytial virus (RSV) infection, respiratory readmissions, use of bronchodilators and other respiratory medications to improve pulmonary symptoms.

Pulmonary function tests (PFTs) were performed at the infant pulmonary function laboratory at OHSU. Eligible survivors living within the Portland, Oregon area had to be at least 3 weeks without a respiratory tract infection or wheezing episode, before testing would be attempted. At the PFT, a history and physical was obtained and details of the infant's respiratory history was recorded, including current medications and known allergies. Infants were sedated with chloral hydrate (50 to 60 mg/kg given orally) after a separate consent was obtained. They were studied supine while quietly asleep. The infant's length, weight, and head circumference were obtained and converted into appropriate z-scores.¹⁶ Tidal volume, respiratory compliance (Crs), and functional residual capacity (FRC) were measured, at 1–2

years of corrected age, with a computerized infant pulmonary function cart (SensorMedics 2600, SensorMedics Inc., Yorba Linda, CA). The measurements were obtained with the infants breathing through a face mask that was connected to a 3-way valve. Crs was obtained with the single-breath occlusion technique and FRC with the nitrogen washout method.^{13,17–22} All measurements were performed by the same technician and over-read by the principal investigator.

Tidal volume was calculated by digital integration of the flow signal as previously described.^{18,22} Briefly, a minimum of 12 flow-volume loops with inspiratory and expiratory volumes within 15% were collected to estimate tidal volumes.^{18,22} For the single-breath occlusion technique,^{17,18,20–23} the airway was briefly occluded at end inspiration until an airway pressure plateau was observed and the Hering Breuer reflex invoked. The linear portion of the passive flow-volume curve was identified, and a regression line drawn to obtain the best fit. From the intercepts on the flow and volume axes, respiratory system compliance was calculated. Acceptance criteria included: 1) stable end expiratory baseline; 2) plateau pressure lasting >100 msec; 3) plateau pressure varying by $< \pm 0.125$ cm H₂O; 4) acceptable flow-volume curve by visual inspection, with linear data segment identified; 5) at least ten breaths accepted with a coefficient of variation <20%.^{13,24}

For the nitrogen washout technique,^{19,20,25–27} calibration was done with 2 known volumes, and a calibration line was constructed for the system at the specific flow rate and used to correlate the nitrogen washed out to the infant's FRC. The system corrected for dead space and corrected the FRC to body temperature, pressure, and water-saturated conditions. Acceptance criteria included: 1) infant supine and quietly asleep; 2) test initiated at end expiration; 3) no evidence of leak on tracing of the washout; 4) consistent tracings; 5) at least 3 measurements with a coefficient of variation <10%.^{13,24}

Statistical Methods

Differences in continuous variables between the two groups were first analyzed by two-tailed, independent samples Student t-tests or the Wilcoxon 2 sample test where appropriate (data not normally distributed). Categorical variables were evaluated with Chi-Square tests and Fisher's exact test where appropriate. Data are presented as mean $\pm$ SD, unless otherwise indicated.

As in the original randomized controlled trial (RCT), the statistical analyses were on intention-to-treat. In our original study, results were adjusted for gestational age at birth, twin gestation, maternal smoking history, rupture of membranes, and gestational diabetes, as these were the initial predictors of interest.¹³ In the current study, comparisons of follow-up pulmonary function testing and clinical respiratory outcomes between groups, were done using mixed linear modeling for continuous variables and generalized estimating equations (GEE) for categorical variables.^{28,29} This approach accounts for the association (non-independence) between twins, and allows for adjustment of additional covariates and potential confounders.^{28,29} Our model included corrected age at the follow-up study, body length at study, and family history of asthma (defined as a positive history of asthma in the mother or father). These covariates were introduced to the model one at a time, and examined for their statistical significance and/or their effect on the relationship between

rescue dose and each outcome. To account for the correlation between twins, mixed linear modeling included family as a random effect, specifying an exchangeable correlation matrix; GEE included siblings as repeated measures for a family, specifying an exchangeable correlation structure. We used SPSS for Windows, Version 22.0, Chicago, IL and SAS 9.1.3, SAS Institute Inc., Cary, NC for analyses.

For our original RCT (primary outcome), we estimated that to show about a 30% difference in Crs between the groups, we would need to study approximately 40 pregnancies in each group to reject the null hypothesis with a type I error of 0.05 and a power of 80%.¹³ For the current follow-up study (secondary outcomes), a post-hoc power analysis estimated that the study had 80% power ($\alpha = 0.05$) to detect a 30% difference in Crs between groups.

RESULTS

A total of 44 mothers with 56 babies were randomized to a rescue course of AS and 41 mothers with 57 babies to placebo. The first 8 patients were recruited at Sacred Heart Hospital, with the remaining patients recruited at OHSU. Neonatal data were not available for one baby in the placebo group, resulting in 56 versus 56 babies available for analysis of the initial hospital stay.¹³ In our original study, we reported no significant differences in maternal and infant characteristics or in survival between groups, except for more maternal smoking by history in the rescue compared to the placebo group (25% versus 5%, $p < 0.05$). There were no significant differences in twin gestation (27% versus 39%), average birth weight (1806 versus 1830 grams), or average gestational age at birth (31.9 versus 32.3 weeks) between the rescue and placebo groups.¹³ As previously reported,¹³ infants in the rescue group had a significantly increased Crs within 72 hours of age and significantly fewer patients in the rescue group required 30% oxygen or 40% oxygen than in the placebo group ($p < 0.05$). There was no significant difference in infants that required surfactant (27% in the rescue versus 39% in the placebo group). Three patients in the rescue and four patients in the placebo group developed bronchopulmonary dysplasia (BPD). There was one neonatal death and one post-neonatal death in the rescue group. Thus, 110 survivors (54 randomized to rescue AS and 56 to placebo) were eligible for assessment of clinical respiratory outcomes with respiratory questionnaires at 1–2 years of age. We obtained follow-up in 87% of these patients (Figure 1). Thirteen patients were ineligible for performance of PFTs due to physical location (follow-up PFTs could only be performed at OHSU) leaving 97 patients eligible for PFTs. We were able to perform follow-up PFTs in 77% of these patients (Figure 1). There was no significant difference in baseline demographics between the patients studied at follow-up and those who were not studied.

Infant characteristics including corrected age at study, length at study, weight, head circumference, race, or gender at the time of follow-up PFTs were comparable between groups. A positive family history of asthma was more common in the placebo group (3% versus 22%, $p < 0.05$) (Table 1). The average weight in both groups was 10.6 kg and length was 78 cm in both groups. There was no significant difference in z-scores for length, weight, or head circumference¹⁶ between the groups (Table 1).

Pulmonary function tests were performed at a mean corrected age of 18.8 months in the rescue AS and 16.6 months in the placebo group (median values 13.1 versus 13.0 months, respectively). PFT measurements were obtained in 40 rescue and 35 placebo patients, a few infants did not have PFT measurements because parents refused sedation or inability to meet the acceptance testing criteria (Figure 1).^{13,24} Table 2 shows the follow-up PFT data. There was no significant difference in tidal volume, total Crs or Crs/kg, and total FRC or FRC/kg between the groups. These differences remained not significant after accounting for the correlation between twins, and using mixed linear modeling to adjust for the potential confounders of: length at time of study, corrected age at study, and family history of asthma. Infants in the rescue AS group had a mean total FRC of 249.4 mL versus 246.2 mL in the placebo group (adjusted 95% CI for difference -15.45 to 38.20; $p=0.37$) (Table 2). Individual measurements of total FRC related to infant length at time of study are presented in Figure 2.

We were able to obtain clinical respiratory outcomes in 49 patients (91%) in the rescue AS group and 47 patients (84%) in the placebo group at 1–2 years of age. We demonstrated no significant differences between the rescue and placebo groups in episodes of wheezing, RSV infection, physician-diagnosed asthma, respiratory readmissions, and use of bronchodilators or other respiratory medications (inhaled and oral corticosteroids) (Table 3). These differences remained not significant after accounting for the correlation between twins, and using GEE to adjust for the important confounding variables of corrected age at study and family history of asthma (Table 3).

DISCUSSION

This follow-up study demonstrates no difference in PFTs (tidal volume, respiratory compliance or functional residual capacity), at 1–2 years of corrected age, in infants born to pregnant women randomized to a single rescue course of AS versus placebo. Clinical respiratory outcomes (assessed with a standardized respiratory questionnaire) also were not significantly different between the groups.

Our original study was a randomized, double-blind, placebo-controlled trial, however we acknowledge some limitations. Preterm delivery is difficult to predict, but 73.5% of our patients delivered at 34 weeks and 88% received the full course of study medication.¹³ Our original study was powered to detect differences in pulmonary function tests at birth (primary outcome), thus assessment of follow-up PFTs and other clinical respiratory outcomes may need a larger sample size. We limited potential confounders such as maternal and delivery factors, postnatal growth, and environmental factors by using a randomized, placebo-controlled study design. Outcomes were assessed blinded to treatment group assignment, eliminating any possibility of expectation bias. The infants mean corrected age at testing was 18.8 months in the rescue versus 16.6 months in the placebo group; however the median age and the infant length at testing were very similar between the groups, so it is unlikely that age confounded our results. Also our follow-up PFTs / clinical respiratory outcomes were adjusted for the correlation between twins and possible confounding by corrected age at study, length at study, and family history of asthma. Finally, we did not

include measurements of peripheral airway function. This will need to be included in future studies.

Growth retardation and changes in lung structure were noted at term after exposure of fetal monkeys to high dose glucocorticoids given at mid-gestation.^{11,12} This resulted in smaller lungs that contained fewer alveoli at term.^{11,12} In preterm sheep, repeat courses of antenatal glucocorticoids have been associated with increased alveolar volume and decreased alveolar numerical density.³⁰ There are few randomized studies in humans reporting follow-up PFTs after a single course of AS therapy,^{31–33} and ours is the first to report follow-up infant PFTs and clinical respiratory outcomes after a single rescue course of AS versus placebo. Normal lung growth and no differences in PFTs (lung volumes and expiratory flows) have been reported in children older than 6 years³¹ and at 10–12 years of age³² following a single course of AS compared to placebo. A 30 year follow-up of a randomized trial of a course of AS showed no differences in spirometry (lung volumes and expiratory flows) between groups.³³ Our findings of comparable tidal volume, Crs and FRC, at 1–2 years, between infants whose mothers were randomized to a rescue course of AS versus placebo is consistent with these studies and indicate that a rescue course is not associated with adverse effects on lung growth / pulmonary function.

Measurements of pulmonary function have been used to quantify the newborn infant's response to different therapeutic interventions including AS therapy.^{13,20,21,27} Studies in humans and animal models demonstrated improvements in respiratory compliance and lung volumes after dosing with AS.^{17,19,34} A single course of AS given within one week of delivery significantly increases Crs and FRC about 50%.^{1,2,19} We reported a significant increase in Crs (20–30%) within 72 hours of birth and decreased oxygen need in newborns whose mothers were randomized to a rescue course of AS versus placebo.¹³ We also recently reported that at the time of discharge from the Neonatal Intensive Care Unit (average postmenstrual age of 36 weeks), there was no significant difference in Crs or FRC between patients in the rescue AS group versus placebo.³⁵ Our current PFT findings extend these early results at hospital discharge and indicate that a rescue course of AS appears to have a time-limited effect on Crs and does not adversely impact infant pulmonary function tests at 1–2 years of age. However, AS are known to induce a cascade/ number of proteins that may have unknown long-term effects, thus continued follow-up is warranted.^{2,3}

Clinical respiratory outcomes including episodes of wheezing, physician-diagnosed asthma, RSV infection, respiratory readmissions, and use of bronchodilators or other respiratory medications were not significantly different between patients in the rescue AS group versus placebo. Our findings are consistent with other randomized studies demonstrating no significant difference in episodes of wheezing^{7,8,36} or in hospital readmissions^{7,8,36,37} through 2–3 years of age, although their report was focused on neurodevelopmental outcomes. These previous studies did not report infant PFTs and also randomized patients to weekly / repeat courses of betamethasone versus placebo^{7,8,37} or a single rescue dose of betamethasone versus placebo.³⁶

Our findings of no difference in tidal volume, Crs, or FRC at 1–2 years of age (secondary outcomes) could have been due to a relatively small sample size or the techniques applied

may not be sensitive enough to show a true difference. However, our findings may indicate that the increased Crs observed within 72 hours of age in the rescue AS group versus placebo is time-limited (dissipation of the beneficial effects of AS on the induction of surfactant), and this improvement is no longer present at 1–2 years. Despite the increased Crs measured within 72 hours of birth in the rescue group, there was no difference in FRC between the groups at this time point. Since all infants had received a single initial course of AS prior to randomization, this supports the premise of a longer term effect of AS on structural lung changes as reflected in FRC measurements.^{13,35} This is consistent with in vitro studies with human lung explants that documented that the biochemical effects of AS begin to decrease 7 days after AS removal, although the corresponding structural changes persist.³⁸ We used the nitrogen washout technique which measures air in communication with the airways. Historically, FRC measurements by nitrogen washout and helium dilution give comparable results,²⁵ and our values are within the range noted in previous studies.^{26,39,40} We did not measure peripheral airway function/ forced expiratory flows, because the raised volume rapid thoraco-abdominal compression technique was not available at our institution at study initiation. Although currently unavailable for clinical use, measurements of pulmonary diffusing capacity for carbon monoxide⁴¹ may have improved our ability to detect a difference between the two groups of patients at follow-up.

Conclusions

A single rescue course of AS versus placebo significantly increases Crs within 72 hours of age and decreases oxygen need in newborn infants, without an adverse impact on pulmonary function tests or clinical respiratory outcomes at 1–2 years of age. These are important data for evaluation of risks and benefits of repeat AS therapy. Longer-term follow-up studies of pulmonary, growth, and neurodevelopmental outcomes are needed.

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Figure 1.

Outline of randomization, treatment, and follow-up of study participants. A few patients in the rescue AS group and in the placebo group did not have PFT measurements because parents refused sedation or due to inability to meet the acceptance testing criteria.^{13,24} Abbreviations: AS, antenatal steroids; PFTs, pulmonary function tests; SHH, Sacred Heart Hospital.

Figure 2.

Total FRC (mL) plotted against length (cm) at time of pulmonary function testing.

Individual data in the cohort of infants randomized to rescue antenatal steroids (open circles) versus placebo (solid triangles) are presented. There was no significant difference in total FRC when both groups were compared when adjusted for body length at PFT, corrected age at PFT, and family history of asthma by mixed linear modeling ($P = 0.37$). Abbreviations: FRC, functional residual capacity; PFT, pulmonary function test.

Table 1

Infant Demographics at Time of Pulmonary Function Testing

	Rescue AS (n = 40)	Placebo (n = 35)	P Value
Corrected age (months) ^a	18.8 ± 12.8	16.6 ± 9.3	NS
	13.1 (12.0–23.1) ^b	13.0 (12.0–16.0) ^b	
Study weight (kg) ^a	10.6 ± 2.3	10.6 ± 2.4	NS
Study weight z-score ^a	−0.02 ± 1.72	0.10 ± 1.44	NS
Length (cm) ^a	77.6 ± 11.1	77.9 ± 9.6	NS
Length z-score ^a	−0.64 ± 2.49	−0.40 ± 1.79	NS
Head circumference (cm) ^{a,c}	46.1 ± 2.1	46.8 ± 1.9	NS
Head circumference z-score ^{a,c}	0.18 ± 1.47	0.22 ± 1.52	NS
Caucasian (%)	38 (95)	33 (94)	NS
Female (%)	23 (58)	18 (51)	NS
Family history of asthma (%) ^d	1/34 (3)	7/32 (22)	<0.05

^a Mean ± SD.^b Median values (25th – 75th percentiles).^c Data available for 30 versus 32 patients.^d Defined as positive history of asthma in the mother or father, data available for 34 versus 32 patients, missing data primarily due to lack of available paternal history.

Abbreviations are: AS, antenatal steroids; NS, not significant.

Table 2**Pulmonary Function Tests in the Two Groups of Infants**

	Rescue AS (n = 40)	Placebo (n = 35)	95% CI^a	P Value^a
Tidal volume (mL)	99.9 ± 28.4	104.7 ± 32.0	(-18.44, 4.26)	0.21
Total Crs (mL/cm H ₂ O) ^b	18.39 ± 6.08	16.82 ± 4.66	(-1.51, 3.25)	0.45
Crs/kg (mL/cm H ₂ O/kg) ^b	1.76 ± 0.47	1.64 ± 0.38	(-0.23, 0.25)	0.93
Total FRC (mL) ^c	249.4 ± 45.3	246.2 ± 73.6	(-15.45, 38.20)	0.37
FRC/kg (mL/kg) ^c	25.3 ± 4.0	24.0 ± 3.5	(-1.61, 3.52)	0.43

Values are mean ± SD and (95% confidence intervals).

^aAdjusted for correlation between twins, corrected age at PFT, length at PFT, and family history of asthma (mixed linear modeling).

^bCrs obtained in 33 and 31 patients and

^cFRC obtained in 30 and 28 patients, respectively.

Abbreviations are: AS, antenatal steroids; Crs, respiratory compliance; FRC, functional residual capacity; PFT, pulmonary function test.

Table 3

Clinical Respiratory Outcomes in the Two Groups of Infants

	Rescue AS (n = 49)	Placebo (n = 47)	Odds Ratio (95% CI)^a	p^a
Episodes of wheezing (%)	15 (31)	22 (47)	0.65 (0.24, 1.75)	0.40
Physician-diagnosed asthma (%) ^b	7 (14)	5 (11)	1.97 (0.42, 9.17)	0.39
RSV infection (%) ^b	3 (6)	6 (13)	0.42 (0.09, 1.88)	0.26
Bronchodilators (%)	14 (29)	16 (34)	1.11 (0.38, 3.27)	0.85
Other respiratory medications (%)	8 (16)	7 (15)	1.70 (0.36, 7.96)	0.48
Respiratory readmissions (%)	8 (16)	8 (17)	1.20 (0.31, 4.60)	0.79

Values are number (%).

^aAdjusted for correlation between twins, corrected age at study questionnaire, and family history of asthma (generalized estimating equations).

^bUnadjusted odds ratio and p values because model would not converge for these variables.

Abbreviations are: AS, antenatal steroids; RSV, respiratory syncytial virus.