Published in final edited form as:

J Pediatr. 2007 April ; 150(4): 345–350. doi:10.1016/j.jpeds.2006.12.013.

Follow-Up Study Of A Randomized Controlled Trial Of Postnatal Dexamethasone Therapy In Very Low Birth Weight Infants: Effects On Pulmonary Outcomes At 8–11 Years Of Age

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Abstract

Objective—To determine if postnatal dexamethasone (DEX) exposure affects pulmonary outcomes at school-age in children born with very low birth weight (VLBW).

Study design—Follow-up study of 68 VLBW children who participated in a randomized controlled trial (RCT) of postnatal DEX. Pulmonary function was assessed by spirometry. Current asthma status was obtained from a parent.

Results—Sixty-eight % of the placebo group had below normal forced expiratory volume in 1 second (FEV₁) compared to 40% of the DEX group ($X^2 = 4.84$, $p = .03$), with trends for lower forced vital capacity (FVC) and FEV₁ values in the placebo group. Fifty % of placebo group and 34% of DEX group had below normal FEV₁/FVC ($X^2 = 1.59$; $p = .21$). Parent-reported prevalence of asthma did not differ between groups. Logistic regression analysis suggested that the positive effects of DEX on pulmonary function at follow-up were mediated in part by shortened postnatal exposure to mechanical ventilation.

Conclusions—Postnatal DEX exposure was associated with higher expiratory flow with no adverse effects on pulmonary outcomes at school-age. The prevalence of asthma and impaired pulmonary function underscore the influence of neonatal illness on health at school age, and stress the importance of repeated follow-up examinations of these children.

Keywords

prematurity; chronic lung disease; bronchopulmonary dysplasia; children; corticosteroid; lung function asthma

Approximately 1.5% of infants are born prematurely each year with very low birth weight (VLBW) (birth weight < 1501 grams) (1), and about 19–23% of these infants will develop chronic lung disease (CLD) (2,3). A diagnosis of CLD has been associated with greater

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edited by AJ and WFB

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hospital readmission rates for respiratory morbidity during the first five years of life (4), increased odds of asthma (4) and respiratory symptoms in childhood (5), and reduced pulmonary function in infancy (6), childhood (7,8), adolescence (9), and young adulthood (10) compared to their VLBW peers without CLD. Systematic reviews indicate that treatment of VLBW infants with corticosteroids, primarily dexamethasone (DEX), in the first few weeks of life significantly decreases duration of ventilator dependence and the incidence of CLD (11–13). The beneficial effects of postnatal corticosteroids on the lung are believed to be related to reduced inflammation (14–16). However, experiments in animals suggest that corticosteroid exposure during critical periods of lung development may impair alveolarization (17–20). Furthermore, follow-up studies of VLBW children suggest adverse effects of postnatal DEX exposure, specifically impaired growth and neurologic development (21–22). These findings led the American Academy of Pediatrics and the Canadian Paediatric Society (23) to recommend against “routine use of systemic DEX for the prevention or treatment of chronic lung disease,” and for additional long-term follow-up of well-designed, randomized, double-blind, controlled trials with no crossover or contamination of treatment.

To date, three studies have examined the long-term effects of postnatal corticosteroid treatment on pulmonary outcomes and growth in school-aged children and adolescents born prematurely with VLBW (24–26). The results are inconsistent—suggesting beneficial (24), adverse (25) and no (24–26) effects of DEX on pulmonary outcomes compared to placebo, and no effects on somatic growth. However, potential effects of DEX on pulmonary outcomes at school-age could have been masked by small sample sizes (24,25) and open-label treatment with DEX in a large proportion (24,26) of children in the placebo group after the initial study period. Furthermore, the early trials were conducted at a time when surfactant was not routinely available. Consequently, the primary purpose of this investigation was to examine the long-term effects of postnatal DEX exposure on pulmonary outcomes in a sample of school-aged children who, as VLBW neonates, received surfactant and participated in a double-blinded, randomized, controlled trial with no contamination of treatment (i.e., no open-label DEX use).

Methods

Participants

Participants were children, 8 to 11 years old, who as neonates participated in a randomized controlled trial of a 42-day tapering course of postnatal DEX to reduce the duration of ventilator dependency (27,28). The children were born between 1992 and 1995, and met the following eligibility criteria: 1) birth weight <1501g; 2) age 15 to 25 days; 3) ventilator dependence without improvement; 4) absence of clinical signs of sepsis; and 5) absence of patent ductus arteriosus by echocardiography. The treatment group received DEX at an initial dose of 0.5 mg/kg/day that was tapered over 42 days. One hundred eighteen infants were randomized and 95 survived to one year of age. Of these “long-term” survivors, 68 (38 DEX, 30 Placebo) agreed to participate in this follow-up study. This study was approved by the Institutional Review Boards of the Wake Forest University Baptist Medical Center and Forsyth Medical Center. Written informed consent was obtained from a parent or legal guardian, and verbal assent was obtained from the child.

Measurements and Procedures

All children reported to the GCRC at the Wake Forest University Baptist Medical Center where height and weight were measured. Body mass index (BMI) (weight in kilograms divided by height in meters squared) was calculated, and percentiles and z-values based on age and sex were determined from National Center for Health Statistics 2000 reference

values (29). The child and parent were then escorted to the Pulmonary Function Lab where pulmonary function testing was conducted.

Pulmonary Function Testing—Forced expiratory flow rates and volumes were obtained via standard spirometric techniques (following the guidelines of the American Thoracic Society) using a Med Graphics Elite Dx System (30). Values were expressed as % of predicted based on published reference data (31), and considered to be abnormal if below the 5th percentile (32,33). Total lung capacity (TLC) and residual volume (RV) were determined from body plethysmography and expressed as a ratio (RV/TLC). Pulmonary diffusing capacity ($D_{L,CO}$) was also determined via the single-breath carbon monoxide technique and corrected for estimated age-specific hemoglobin levels (34).

Asthma diagnosis and airway reactivity—Children were categorized as having asthma if the parent or guardian reported that the child had asthma and/or used medications for asthma treatment. A subsample of children also underwent maximal progressive exercise testing on a cycle ergometer as part of the larger study. Spirometry was repeated immediately and 5 minutes post-exercise, as well as 20 minutes following three puffs of albuterol delivered with a spacer. A 15% decrease in FEV₁ from pre-exercise values was the criterion used to define exercise-induced bronchoconstriction (35). A 12% increase in FEV₁ from pre-exercise levels was considered to be a positive bronchodilator response (36).

Neonatal characteristics—Neonatal data regarding birth weight, gestational age, antenatal steroid exposure, and number of days of mechanical ventilation and supplemental oxygen post-randomization were obtained from medical records by research nurses. Gestational age was based on the date of the mother's last menstrual period, or, if not available, the obstetrician's estimate, or if no prenatal estimate was available, neonatal assessment. Birth weight z-values and percentiles (based on sex and gestational age) were derived from the reference data of Oken et al. (37). An infant was considered small for gestational age (SGA) if birth weight was less than the 10th percentile for gestational age. A diagnosis of CLD was defined as the use of supplemental oxygen at 36 weeks post-menstrual age (38). Treatment assignment (DEX or Placebo) was obtained from the research database. All testers, children, and their parents were blinded to treatment assignment.

Data analysis—Based on exploratory analyses, nonparametric statistics were used to describe central tendency and dispersion (i.e., median, 5th and 95th percentiles). Mann-Whitney U and chi square tests were used to compare DEX and Placebo groups for continuous and categorical variables, respectively. Spearman correlation coefficients were used to examine relationships between neonatal characteristics and pulmonary function at school-age. Logistic regression analysis was used to examine possible mediators of the effect of DEX on pulmonary function. Cochran-Mantel-Haenszel techniques were used with stratified analysis to develop common odds ratios and test for conditional independence. The Breslow-Day test was used to test for homogeneity of stratum-specific odds ratios.

Results

Sixty-eight of 95 surviving children (38 DEX, 30 Placebo) underwent follow-up evaluation. Of the remaining 27 children, 12 subjects could not be located, 1 subject declined participation, 5 parents declined participation, and 9 subjects agreed to participate but were unable to keep appointments (Figure). Neonatal characteristics were compared between surviving participants and nonparticipants and no differences were found. Participants' neonatal characteristics are presented in Table I. Ninety-two percent of the DEX group and 83% of the Placebo group were born with extremely low birth weight (< 1001 g). Birth weight, birth weight z-value, and gestational age did not differ significantly between the

treatment groups. No children in the DEX group and two in the Placebo group were small for gestational age. Treatment (DEX or placebo) was initiated at a median age of 19 days in both groups. Subjects in the DEX group received mechanical ventilation and supplemental oxygen for significantly fewer days than those in the placebo group. Fifty percent of the children in the DEX group and 73% in the Placebo group had a diagnosis of CLD ($p = .05$). All children were treated with surfactant.

Participants' characteristics at follow-up evaluation are presented in Table II. All children were between 8 and 10 years of age except for one child who had to be rescheduled shortly after he turned 11 years-old. The DEX and Placebo groups did not differ in current age, weight, height, or body mass index.

Pulmonary function

Sixty-three of the 68 children (35 DEX, 28 Placebo) were able to perform spirometry adequately. Five children (3 DEX, 2 Placebo) were unable to perform spirometry sufficiently due to cognitive delay ($n=4$) or physical limitations associated with cerebral palsy ($n=1$). As shown in Table III, average values for FEV₁ and FVC were not statistically different between the two treatment groups. However, a significantly ($p=.03$) greater proportion of the children in the Placebo group had an FEV₁ below normal ($< 5^{\text{th}}$ percentile) compared to the children in the DEX group (68% v. 40%, respectively). The FVC was below normal in 36% of the children in the Placebo group and 17% of the DEX group ($p=.08$). The ratio of FEV₁ to FVC did not differ between groups, with 34% of the DEX group and 50% of the Placebo group having ratios below the 5th percentile ($p=.21$). There was also no significant difference in FEF₂₅₋₇₅ between the two groups. The results did not change appreciably when using the cutoffs of 80% of predicted for FVC and FEV₁ and 60% for FEF₂₅₋₇₅ that are commonly used in the clinical setting as the lower limits of normal (39). Stratification by antenatal steroid exposure did not affect results significantly. Logistic regression analysis revealed that DEX was associated with significantly reduced odds of having below normal FEV₁ compared to the Placebo group (OR = 0.32, 95% confidence interval (CI): 0.11, 0.90). Inclusion of either duration of mechanical ventilation (MV) or supplemental oxygen (O₂) in the neonatal period attenuated the association between DEX and FEV₁ (Adjusted OR_{MV} = 0.41; 95% CI: 0.14, 1.23; and OR_{O2} = 0.36; 95% CI: 0.12, 1.07). The majority of children (50/68) had difficulty performing plethysmography and the single-breath diffusion maneuver; consequently, total lung capacity, residual volume, and diffusion capacity were not analyzed.

Airway responsiveness to exercise and bronchodilator therapy did not differ between DEX and Placebo groups, as shown in Table II. Seven percent of both groups exhibited exercise-induced bronchoconstriction ($\geq 15\%$ decrease in FEV₁). Twenty percent of the DEX group and 23% of the Placebo group exhibited a positive bronchodilator response ($\geq 12\%$ increase in FEV₁). The post-bronchodilator improvement in FEV₁ reduced the number of subjects in the placebo group with below normal function from 68% to 37%, and the DEX group demonstrated a slight increase (40% to 44%). Three children in the DEX group and two children in the Placebo group had significant decreases in FEV₁ ($>12\%$) following bronchodilator therapy. Finally, current asthma determined by parental report of diagnosis and asthma medication use did not differ between DEX and placebo groups.

Discussion

The results of this study suggest that postnatal DEX treatment in VLBW infants does not adversely affect pulmonary function at school age and may impart some benefit. A greater proportion of children who received postnatal DEX exhibited normal spirometry compared to children who received placebo. These results are consistent with the short-term benefits of

DEX on pulmonary outcomes in the neonate, including decreased inflammation (14–16), decreased duration of mechanical ventilation and supplemental oxygen dependence (11–13), and improved lung mechanics (40,41). The results of multivariate analysis suggest that the long-term beneficial effects of DEX on pulmonary function at follow-up were mediated, at least in part, by the acute beneficial effects on the neonatal lung (i.e., decreased duration of ventilation and supplemental oxygen use) observed in DEX-treated children.

Comparisons with previous studies are difficult due to differences in study design and DEX exposure, including dose and duration. The randomized controlled trial in which our sample participated, as infants, was modeled after the study of Cummings et al. (42) which demonstrated significant improvements in pulmonary outcomes (faster weaning from mechanical ventilation and supplemental oxygen) in infants receiving a 42-day tapering course of DEX compared to placebo. However, in contrast to our study, follow-up evaluation of their participants at 15 years of age revealed no long-term differences in pulmonary function between the children treated with DEX (n=9) vs. placebo (n=4) (25). The lack of group differences may be due to limited statistical power associated with their small sample size.

Mieskonen et al.(24) found significantly higher FVC in 7.8 to 9.2 year-olds treated postnatally with one week of DEX (n=8) compared to those given placebo (n=8). However, forced expiratory flow rates did not differ between treatment groups, possibly because of limited statistical power. In the largest follow-up study to date, Jones (26) reported pulmonary function in 142 thirteen to seventeen year-old children who participated as infants in the Collaborative Dexamethasone Trial (43), a multi-center, postnatal randomized controlled trial of one-week of DEX treatment. Despite observing beneficial effects of DEX in the postnatal period (i.e., fewer days of ventilator dependence)(43), no differences were noted at follow-up between DEX (n=68) and placebo (n=74) groups for FVC, FEV₁, FEV₁/FVC, FEF_{25–75}, peak expiratory flow rate or bronchodilator responsiveness, or in respiratory morbidity (current asthma, wheezing, coughing, inhaler use). However, a large proportion of the placebo group in this study (39%), as well as the study by Mieskonen et al. (50%), were exposed to open-label DEX treatment after the initial study period which may have attenuated possible treatment effects.

Differences in sample characteristics (both postnatal and current) also make comparisons with previous studies somewhat difficult. Our participants were born in the post-surfactant era and were generally smaller, more premature and had a higher incidence of CLD than participants in the studies by Jones (26) and Mieskonen et al. (24). As neonates, all were dependent on mechanical ventilation compared to only two-thirds in the study by Jones. In general, these differences suggest that our participants may have had greater risk for poor pulmonary outcomes compared to those in the studies by Jones (26) and Mieskonen et al. (24), and therefore more likely to benefit from DEX treatment (44). At follow-up evaluation, our participants were similar in age to those of Mieskonen et al. (24) and younger than the adolescents studied by Jones (26) and Gross et al.(25). It is possible that treatment group differences observed in childhood may resolve with subsequent growth and maturation.

Although DEX was associated with better pulmonary function, 40% of the DEX group (and 68% of the placebo group) had below normal FEV₁, suggesting larger airway obstruction. However, lack of significant group differences in the FEV₁/FVC suggests that the lower FEV₁ values may be attributed to the somewhat lower FVC in the placebo group, and possible airway restriction. Unfortunately, we were unable to determine lung volumes in the majority of children, and can not be certain whether the reduced values are due to mild restriction, or secondary to airway obstruction and air trapping. The finding that 50% of the placebo group and 34% of the DEX group had FEV₁/FVC values below the 5th percentile

suggests that compromised larger airway function is the more likely explanation. The positive bronchodilator response exhibited by a portion of both groups suggests some reversibility of airway obstruction. Furthermore, the large proportion of children in both groups with below normal FEF₂₅₋₇₅ % predicted values implies smaller airway obstruction, but may also be due to reduced FVC and TLC.

The prevalence of asthma did not differ between treatment groups. Approximately one-third of the children in each group had asthma as reported by the parent. This finding is consistent with that reported by Jones in the Collaborative DEX Trial follow-up study (26). Reliance on parental report may underestimate the prevalence of asthma or pulmonary limitations as evidenced by the considerable number of children with below normal pulmonary function. The positive bronchodilator response observed in about 20% of the children suggests that some of the reduced pulmonary function may be ameliorated by pharmacologic intervention. Further investigation is needed to substantiate the prevalence of asthma and the extent to which reduced pulmonary function is reversible with appropriate asthma therapy.

We were also not able to determine the potential effects that postnatal DEX may have had on the lungs' diffusing capacity because the majority of children could not perform the single-breath D_LCO maneuver adequately. In animal models, DEX has been shown to impair septation and alveolarization (17–20). Mitchell et al. (45) reported impaired gas transfer at rest and during exercise as measured by D_LCO in prematurely-born children with BPD but not in those without BPD. Consequently, the negative effects that DEX may have on alveolarization may be countered by its positive effects of reducing exposure to mechanical ventilation and supplemental oxygen, and the subsequent risk for BPD.

Neonatal DEX exposure has been associated with impaired somatic growth early in life (17–20), and concomitant lung growth may also be impaired. A study by Yeh et al. (46) suggested that long-term growth impairment was associated with postnatal DEX exposure at 6 years of age. In contrast, the results of the current study as well as other follow-up studies (24–26) show no long-term differences between DEX and placebo-treated subjects for weight and height measured during childhood (24) or adolescence (25,26). However, without measurement of total lung capacity at follow-up, it is not possible to determine if somatic and lung growth were discordant.

Major strengths of this study are the absence of crossover or contamination of treatment following the postnatal randomized controlled trial, and a fairly large sample size for a single-center study. However, we do recognize that with a follow up rate of 72%, the potential exists for bias due to lost-to-follow-up. Our results may have also been affected by survivor bias due to a trend for higher mortality in the placebo group and the expectation that infants who died would have had worse pulmonary function had they survived. In addition, we did not have information on maternal smoking or asthma, or current smoke exposure in the children, all of which may affect pulmonary outcomes in these children, although we expect that these factors were balanced by randomization (47–49). The generalizability of our study may be limited by the sample being drawn from a single center and the use of a course of DEX that is longer in duration than that reported in a recent cohort study of VLBW infants (50).

Despite these limitations, the results of this study may have clinical implications related to the use of corticosteroids to prevent CLD in premature infants. We found no adverse long-term effects of postnatal DEX exposure on forced expiratory flow rates and volumes, airway reactivity, and parental report of asthma in 8–11 year-old children born prematurely with VLBW. Our finding that a large proportion of the children had below normal pulmonary function and parent-reported asthma illustrates the influence of neonatal illness on health at

school age, the importance of surveillance to identify affected children, and the need for the best possible interventions to prevent CLD. Future studies of children who participated in randomized trials of postnatal steroids should include examination at an older age when reliable measures of lung volumes and diffusion capacity can be obtained, and more focused evaluation for the presence of asthma.

Acknowledgments

This research was supported by the General Clinical Research Center of Wake Forest University Baptist Medical Center grant number M01-RR07122, NIH grant number P01 HD047584, the Intramural Research Support Committee of Wake Forest Medical School and the Brenner Center for Child and Adolescent Health.

We are grateful to Ms. Alice Scott RN, the GCRC nurses, the pulmonary function laboratory technicians, students in the Health & Exercise Science Undergraduate and Graduate programs, and the children and their families for making this project possible.

Abbreviations

VLBW	Very low birth weight
CLD	Chronic lung disease
SGA	Small for gestational age
PFT	Pulmonary function testing
FVC	Forced vital capacity
FEV ₁	Forced expiratory volume in 1 second
FEF ₂₅₋₇₅	Forced expiratory flow between 25 and 75% of FVC
RV	Residual Volume
TLC	Total lung capacity
D _{L,CO}	Carbon monoxide diffusing capacity
BPD	Bronchopulmonary dysplasia

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Figure.

Table 1

Neonatal characteristics expressed as median, (*5th*, *95th* percentiles), or proportion.

	DEX	Placebo
n	38	30
Gestational age, wks	25.0 (23.0, 28.1)	26.0 (23.6, 29.9)
Gender, % male	44%	53%
Race, % Caucasian ^a	65%	47%
Birth Weight, g	743 (523, 1172)	789 (557, 1293)
Birth Weight z-value	-0.14 (-1.15, 1.06)	-0.24 (-1.47, 0.66)
Mechanical Ventilation, days ^{b,c}	10 (1, 45)	24 (2, 68)
Supplemental Oxygen, days ^{b,c}	45 (6, 315)	99 (24, 549)
+ CLD diagnosis, % ^d	50%	73%

^a Non-Caucasians were African-American except one Latino child in the DEX group

^b Days post-randomization

^c p<0.05

^d p=0.05

Table 2

Participants' characteristics at follow-up evaluation expressed as median (*5th, 95th percentiles*), or proportion

	DEX	Placebo
Age, yrs	9 (8, 10)	9 (8, 10)
Weight, kg	32.1 (19.7, 51.9)	28.6 (19.8, 73.1)
Weight z-value	0.31 (−2.63, 2.31)	−0.68 (−2.94, 3.04)
Height, cm	136.7 (117.3, 147.2)	134.4 (116.5, 152.9)
Height z-value	0.05 (−2.45, 1.94)	−0.28 (−2.66, 2.57)
BMI, kg/m ²	17.2 (14.3, 25.2)	15.5 (13.2, 32.6)
BMI z-value	0.35 (−1.43, 2.16)	−0.55 (−2.42, 2.54)
Asthma by parent report, %	29	33

All n.s.

Table 3

Pulmonary function by treatment group expressed as median^a (5th, 95th percentiles)

	DEX	Placebo	p Value
n	35	28	
FVC, % pred	94 (72, 124)	89 (65, 141)	0.08
FEV ₁ , % pred	86 (49, 112)	76 (52, 126)	0.08
FEV ₁ /FVC, %	81 (63, 98)	80 (65, 100)	0.71
FEF ₂₅₋₇₅ , % pred	68 (23, 136)	61 (23, 96)	0.49
Change in FEV ₁ post-exercise, % ^b	2 (-18, 18)	2 (-24, 16)	0.51
Change in FEV ₁ post-bronchodilator, % ^c	3 (-20, 39)	7 (-35, 40)	0.96

^a Mann-Whitney U test used to compare groups.

^b n=56

^c n=53