A Prospective, Randomized, Double-Masked Trial Comparing Low Dose to Conventional Dose Dexamethasone in Neonatal Chronic Lung Disease

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Abstract

Aim: To determine if low dose dexamethasone for the treatment of chronic lung disease would be as effective as high dose with less adverse effects.

Methods: A prospective, randomized, double-blinded trial of infants ≤1500 grams, ≤34 weeks, and ≤28 days of age. The high dose group received 0.5 mg/kg/d of dexamethasone for three days followed by 0.3mg/kg/d for four days. The low dose group received 0.08 mg/kg/d of dexamethasone for seven days.

Results: Infants in the low and high dose groups had similar weights, gestational ages at birth, male to female ratios, and entry FiO_2. The groups were similar in terms of proportion extubated during steroid course, change in FiO_2, O_2 requirement at 36 weeks, hospital days, ventilator days, and effect on the hypothalamic-pituitary-adrenal axis. The high dose group had significantly more patients who required treatment for hypertension and more abnormal neurodevelopmental outcomes at one year adjusted age. The high dose group also had slower weight gain, slower head growth, more patients with hyperglycemia, and a smaller mean head circumference at one year adjusted age, although these differences did not reach statistical significance.

Conclusions: Compared to low dose dexamethasone, conventional dosing was associated with similar pulmonary outcomes and more adverse side effects.

INTRODUCTION

Dexamethasone therapy has been used in various dosing regimens to prevent or treat chronic lung disease in preterm infants. Dexamethasone treatment has been shown to decrease oxygen and ventilator requirements with an improvement in pulmonary function, lung mechanics, and gas exchange.[1,2,3,4] However, concern exists about the adverse effects of dexamethasone on preterm infants treated for chronic lung disease, especially regarding neurodevelopmental outcomes.

A recent metaanalysis of forty studies and 4,148 infants found a significantly increased risk of adverse neurodevelopmental outcome in infants who had received dexamethasone.[5] Although widespread use of dexamethasone for preterm infants at risk for chronic lung disease was not recommended given the increased risks, the author noted the need for more studies evaluating the minimum effective dose[5]. The starting dose of dexamethasone was similar across the trials included in the metaanalysis, with 29 of 40 studies using 0.5 mg/kg/d (range, 0.15 mg/kg to 2 mg/kg).[5] Although treatment courses ranged from 3 days to 42 days, the authors noted that very short dexamethasone courses (1 to 3 days) did not demonstrate any significant beneficial effect on chronic lung disease, while there was no evidence to support an added benefit of courses lasting longer than 7 days.[5]

We hypothesized that a seven day dexamethasone course of 0.08 mg/kg/d would be as effective for the treatment of chronic lung disease as one with a starting dose of 0.5 mg/kg/d, with less adverse effects. The primary outcome of

this prospective, randomized, double-masked, controlled trial was to compare the adverse side effect profile of the dosing groups.

PATIENTS AND METHODS

Infants <34 weeks gestational age and <28 days of age with birth weights ≤ 1500 grams were eligible if they were ventilator dependent with an $FiO_2 \geq 0.40$, and treating physicians considered steroid treatment to be clinically indicated. Infants with complex congenital anomalies, chromosomal anomalies, necrotizing enterocolitis, or culture proven sepsis were excluded from the study. Infants who had already received any corticosteroid treatment were excluded from the study. After informed consent was obtained, infants enrolled in the study were randomly assigned to either low dose or high dose dexamethasone with birth weight stratification. The low dose group received seven days of 0.08 mg/kg/d of dexamethasone. The high dose group received 0.5 mg/kg/d of dexamethasone for three days followed by 0.3mg/kg/d for four days. The daily dose for each group was divided into two doses given every 12 hours.

The infants were stratified into three groups according to their birth weight: less than 750, 751-1000, and 1001-1500 grams. Physicians and nurses were blinded regarding the dose administered. Only the study pharmacist, who has no clinical involvement with infants, was aware of the doses administered. The research protocol was approved by the Institutional Review Board at Loyola University Medical Center.

Clinical care was performed at the discretion of the attending neonatologists. For all infants, supplemental oxygen and mechanical ventilation were adjusted to maintain an oxygen saturation within 88-96%. All infants had received surfactant therapy (Beractant, Ross Laboratories, Columbus, Ohio) according to dosing guidelines. Blood gas measurements and chest radiographs were obtained as clinically indicated. Nutritional and metabolic support followed our nursery routine, which included parenteral nutrition by day 2 of age. Enteral feeding was introduced and advanced as tolerated. Breast milk fortifier or 24 calorie/ounce formula was begun when enteral feedings reached 100cc/kg/d.

Diuretics, bronchodilators, and methylxanthines were used as clinically indicated. Treating physicians decided when extubation was indicated. However, extubation criteria were given as parameters at which extubation was mandatory in infants ≥750 grams. On the pressure-limited ventilator, extubation was mandatory in infants ≥750 grams if peak inspiratory pressure ≤16, mean airway pressure ≤ 7, rate ≤20, and FiO_2 ≤0.30 (Sechrist Industries, Inc., Anaheim, CA, and Servo 300, Siemens Medical Systems, Inc., Malvern, PA). On the high frequency oscillator, extubation was mandatory in infants ≥750 grams if Delta P was < 16, mean airway pressure was ≤7, and FiO_2 was ≤0.30 (Sensormedics 3100A, Viasys Inc., Yorba Linda, CA). Infants <750 grams were allowed to remain ventilated at the discretion of the attending neonatologist. Treating physicians could also decide to retreat with dexamethasone if clinically indicated by degree of pulmonary disease.

Infants were followed and analyzed for the following adverse side effects (primary outcome criteria):

1. Suppression of Hypothalamic Pituitary Adrenal (HPA) Axis: Serum cortisol levels were measured at 10:00 AM before dexamethasone administration and at 10:00 AM three days after completion of the seven day course of dexamethasone. After each 10:00 AM blood draw 3.5 mcg/kg of 1-24 corticotropin (Cortosyn®, Organon INC, West Orange, NJ) was administered, and serum cortisol levels were redrawn thirty minutes later in order to assess the hypothalamic-pituitary axis.[6, 7] Serum cortisol was analyzed by the equilibrium dialysis radioimmunoassay (Quest Diagnostics, Wallingford, CT).

2. Cardiomyopathy All study infants had baseline echocardiograms to evaluate for ventricular hypertrophy at study entry and repeat echocardiograms done at completion of dexamethasone course.

3. Hyperglycemia Hyperglycemia was defined as blood glucose > 150 mg/dl. Blood glucose was checked on the day of study entry and followed during the seven day course. Decision to start insulin therapy was made by the treating physicians.

4. Hypertension Hypertension was defined as systolic blood pressure greater than 2 standard deviations above the mean for gestational age confirmed by two measurements. Infant blood pressure was assessed daily.

5. Poor weight gain Weight, length, and head

circumference were measured on the day of study entry and at the end of the seven day course. Weights were measured daily during the dexamethasone course.

Medical records were reviewed to obtain the following data: patient demographics, including gestational age, birth weight, sex, apgar scores, day of life at study entry, weight, length, and head circumference, survival without supplemental oxygen at 36 weeks postmenstrual age, number of days on ventilator, number of days on oxygen supplementation, number of hospital days, and mortality. Data also included incidence of intraventricular hemorrhage, necrotizing enterocolitis, gastrointestinal perforation, pneumothorax, and retinopathy of prematurity requiring laser photocoagulation. Cranial ultrasonography was performed on all infants at day seven and day twenty-eight of life.

All infants with a birth weight <1250 grams are tracked in our outpatient follow-up program through three years of age. Medical records from this clinic were reviewed to obtain head circumference and neurodevelopmental data at one year adjusted age. Neurodevelopmental status of study infants was assessed by a neonatologist and a physical or occupational therapist using the modified Gesell Developmental Appraisal. Evaluation was performed without knowledge of amount of dexamethasone received.

STATISTICAL ANALYSIS

For our study we calculated our sample size based on the incidence of side effects. Based on previous data, we expected a 50% decrease in side effects in the control group.[8] A sample of 30 subjects per group was required to give an 80% probability of detecting a difference in side-effect rate of 20% in the experimental group, with a type 1 error of 0.05.[9] Data were analyzed using the Fisher exact test, the two-tailed Student t-test, and the two-tailed T-Test for paired samples. The Newcombe-Wilson method without continuity correction was used to calculate confidence intervals for the risk difference (RD) between two proportions. The study was halted after 17 infants had been enrolled.

RESULTS

This study was designed before the recommendations against dexamethasone use in infants had been established. Although the study design called for thirty infants per group, the study was terminated prematurely following the 2002 statement from the American Academy of Pediatrics and the Canadian Paediatric Society regarding postnatal use of systemic dexamethasone for the prevention or treatment of chronic lung disease. The statement outlined criteria for use and directed that the primary outcome of controlled trials be survival without long-term developmental impairments.[10]

Study recruitment continued from October 2000 through February 2002. After randomization, eight infants were assigned to the low dose group, and nine infants were assigned to the high dose group. One infant from each treatment group expired. The infant in the high dose group died on the second day of the steroid course at 10 days of life due to extreme prematurity; his results were not included in the outcome analysis. The infant in the low dose group died at four months of age in the emergency room after suffering a cardiopulmonary arrest at home one month after discharge. Her results were included in the outcome analysis.

Two of the eight infants in the high dose group were withdrawn from the study on day six of the seven day dexamethasone course for complications. One infant was withdrawn secondary to severe ventricular hypertrophy, and another was withdrawn secondary to recalcitrant hypertension. The data from these two infants were included in the analysis. The inclusion of these infants having had received less than the total steroid dose could only dilute the adverse effect profile and would not increase significance of effects in the high dose group.

Patient demographics were similar between groups (Table I). Infants in the low and high dose groups had similar birth weights (773 ± 182g vs. 767 ± 149g,) gestational ages at birth (26.1 ± 1.8 vs. 25.8 ± 0.9 wks), male to female ratios, and entry FiO_2 (0.52 ± 0.16 vs. 0.57 ± 0.08), respectively. In the low dose group, the mean age dexamethasone was started was 16.8 ± 5.7 days with a range of 8-24, and in the high dose group, the mean was 14.8 ± 6.5 days with a range of 5-27. Maternal demographics, including prenatal steroid treatment, were similar between groups.

Figure 1

Table I: Patient Demographics

	High Dose	Low Dose	P value
Mean Birth Weight (grams)	766	773	0.94
Mean Gestational Age (weeks)	25.8	26.1	0.62
Male:Female	1:1	1:1	>0.99
Less than 750 grams	4/8	4/8	>0.99
751-1000 grams	4/8	3/8	>0.99
1001-1500 grams	0/8	1/8	>0.99
Entry FiO2	0.57	0.52	0.42
Maternal steroids received	6/8	5/8	>0.99
Maternal Age	25.8	26.1	0.62
Surfactant (beractant) doses	2.6	2.5	0.74
Mean day of age on study entry	14.8	16.8	0.52

Compared to low dose, treatment with high dose dexamethasone had similar effect on pulmonary symptoms (Table II). The low dose and high dose groups were similar in terms of survival, proportion extubated during steroid course, change in FiO_2, O_2 requirement at 36 weeks postconceptual age, total hospital days, and days of mechanical ventilation. Each group received similar subsequent dexamethasone courses in terms of total dose per body weight (mg/kg), additional treatment days, and total additional doses.

Figure 2

Table II: Pulmonary effects

	High Dose	Low Dose	P value
Extubated during dexamethasone (DEX) course	3/8	4/8	0.61
Mean Change in FiO2	0.25	0.16	0.21
O2 requirement at 36weeks post menstrual age	7/8	5/8	0.25
Chronic lung disease medications at discharge	7/8	4/8	0.28
Total hospital days	91.88	92	>0.99
Total ventilator days	38.25	43	0.65
Received subsequent DEX for chronic lung disease	7/8	4/8	0.28
Total additional DEX (mg/kg)	2.4	2.1	0.81
Total additional days of DEX	8.9	6.1	0.52
Total additional doses of DEX	13.4	11.4	0.77
O2 dependent at six months adjusted age	1/8	1/8	>0.99
Adjusted Age at Discharge (weeks)	38.68	39.29	0.72
Adjusted Age at room air (weeks)ª	41.8	40.6	0.72

ª Does not include 2 infants (1 from each group) on home O2 at 6 months

Compared to the low dose group, the high dose group had a more adverse side effect profile (Tables III and IV). The high dose group had significantly more infants who required treatment for hypertension (4/8 vs. 0/8). This difference represents an absolute risk increase in hypertension of 50%

compared to low dose treatment (Confidence Interval (CI) 0.15 to 0.85). The high dose group also had more patients who developed hyperglycemia (3/8 vs. 0/8), slower weight gain during treatment (2.14 vs. 7.32 g/kg/d), slower head circumference growth during treatment (0.8 vs. 1.3 cm/week), and a smaller mean head circumference at one year adjusted age (44.7 vs. 46.7 cm), although these differences did not reach statistical significance. Incidence of other adverse effects, including ventricular hypertrophy, hypothalamic-pituitary-adrenal axis suppression, and intraventricular hemorrhage, was similar between the groups. There was no significant difference in the incidence of secondary outcomes, including necrotizing enterocolitis, gastrointestinal perforation, pneumothorax, and retinopathy of prematurity requiring laser photocoagulation.

Figure 3

Table III: Adverse side effects

MEANS	High Dose	Low Dose	P value
Weight Gain (g/d)	11.88	20.00	0.85
Weight gain (g/kg/d)	2.14	7.32	0.76
Change in Head Circumference (cm/week)	0.8	1.1	0.12
PreDEX baseline cortisol (mcg/dL)	7.5	8.5	0.74
PreDEX cortisol after ACTH (mcg/dL)	15.13	15.63	0.87
PostDEX baseline cortisol (mcg/dL)	4.14	8.25	0.18
PostDEX cortisol after ACTH (mcg/dL)	16.14	14.14	0.59
Head Circumference at 40 weeks adjusted age (cm)	37.1	36.3	0.62
Head Circumference at 1 year adjusted age (cm)	44.7	46.7	0.25

Figure 4

Table IV: Risk difference (RD) with high dose dexamethasonea

	High Dose	Low Dose	RD	95% CI
Moderate-severe ventricular hypertrophy	1/8	0/8	0.13	-0.22 to 0.47
Mild ventricular hypertrophy	0/8	2/8	-0.25	-0.59 to 0.12
Intraventricular hemorrhage Grade 3 or 4	2/8	3/8	-0.13	-0.49 to 0.29
Gastrointestinal bleeding or perforation	0/8	0/8	0	-0.32 to 0.32
Laser photocoagulation for retinopathy of prematurity	3/8	1/8	0.25	-0.17 to 0.59
Gastrointestinal perforation	0/8	0/8	0	-0.32 to 0.32
Death	1/9	1/8	-0.14	-0.36 to 0.36
Blood glucose >150	3/8	0/8	0.38	-0.03 to 0.70
Blood Pressure >2 Standard deviations	4/8	0/8	0.50	0.15 to 0.85
Rx given for hypertension	4/8	0/8	0.50	0.15 to 0.85
Mild – Moderate developmental delay at 1 year adjusted age	4/8	1/6	0.33	-0.16 to 0.65
Severe developmental delay at 1 year adjusted age	1/8	0/6	0.13	-0.28 to 0.47
Abnormal neurodevelopmental outcome at 1 year adjusted age	5/8	1/6	0.46	-0.01 to 0.74

aIf RD<0, RD = Absolute Risk Reduction. If RD>0, RD=Absolute Risk Increase.

Neurodevelopmental evaluation at one year adjusted age was available for fourteen infants. Five of eight infants in the high dose group and one of six infants in the low dose group had abnormal neurodevelopmental outcomes at one year adjusted age. Compared to low dose treatment, the absolute risk increase in abnormal neurodevelopmental outcomes with high dose treatment was 0.46 (CI= –0.01 to 0.74). Four infants in the high dose and one in the low dose group had mild to moderate neurodevelopmental delay at one year adjusted age (RD= 0.33, CI= -0.16 to 0.65). The mild neurodevelopmental delays included delays in language and gross motor skills. One infant in the study had severe neurodevelopmental sequelae with blindness.

DISCUSSION

Chronic lung disease occurs in premature infants with severe hyaline membrane disease who require treatment with mechanical ventilation and oxygen. The incidence of chronic lung disease is dependent on birth weight; as a greater number of very low birth weight (<1500grams) infants survive, particularly those <1000 grams, the burden of this morbidity on neonatal survivors will continue to increase. The pathogenesis of chronic lung disease is not only related to mechanical ventilation and free radical injury. A more likely scenario involves an inflammatory response that predisposes the immature lung to postnatal barotraumas, as well as oxidant and infectious injuries.[11, 12]

As inflammation is a significant contributing factor in the development of alveolar and airway damage, therapy against inflammatory mediators could help in the treatment of chronic lung disease. Corticosteroids have been associated with numerous potential physiologic benefits on the lung, including increased surfactant synthesis, enhanced beta-adrenergic activity, increased antioxidant production, stabilization of cell and lysosomal membranes, and inhibition of prostaglandin and leukotriene synthesis.[13] Acute improvement in dynamic lung compliance as well as decreased pulmonary resistance have also been demonstrated with dexamethasone treatment.[3] As this acute improvement in lung function facilitates weaning from mechanical ventilation, postnatal steroids have been widely used for chronic lung disease.

Several investigators have shown that treatment of chronic lung disease with dexamethasone produces an improvement in oxygen and weaning from assisted ventilation with earlier extubation compared to placebo.[2, 4, 14,15,16,17] These studies used 0.5 mg/kg - 1 mg/kg/d with a tapering regimen over 12 to 42 days. The starting dose of dexamethasone in a recent metaanalysis of 40 studies was similar across the trials, with 29 of 40 studies using 0.5 mg/kg/d (range, 0.15 mg/kg to 2 mg/kg).[5] These high doses were associated with many serious adverse effects like hyperglycemia, hypertension, gastrointestinal bleeding and perforation, hypertrophic cardiomyopathy, a significant decrease in weight gain, suppression of the hypothalamic-pituitary-adrenal axis, and adverse effects on the developing brain. [2, 4, 14, 15, 18,19,20,21,22,23,24] In 2002 the American Academy of Pediatrics and the Canadian Paediatric Society concluded that dexamethasone treatment of infants is associated with an increased risk of short- and long-term complications, including impaired somatic and head circumference growth and neurodevelopmental delay.[10]

The dexamethasone dose of 0.5 mg/kg/d, which was used in our intensive care unit and many centers across North America at the time of the study conception, was published originally by Avery et al. in 1985.[2] There were no dose response studies done to come up with this dose, which is about 10-15 times higher than the equivalent basal secretory rate of cortisol.[25] The dose is also much higher than anti-inflammatory dose of 0.08-0.3 mg/kg/d of dexamethasone used in the pediatric population.[26, 27] In 2001, Stark et al

reported use of a lower dexamethasone dose of 0.15 mg/kg/d, which showed improvement in lung disease, but was associated with adverse side effects including gastric perforation, hypertension, hyperglycemia requiring insulin, and decreased weight and head circumference at 36 weeks' postmenstrual age.[28] These data followed a preliminary report published in 1999.[29] We chose a dose of 0.08 mg dexamethasone/kg/d because it is twice the basal secretory rate of cortisol and half the amount originally reported by Stark in 1999. At the time of study conception, the extent of the risks of dexamethasone was not established, and a placebo arm was not incorporated into the study.

We speculated that a low dose of dexamethasone would minimize short- and long-term side effects while being as effective as the high dose in improving pulmonary mechanics and gas exchange. A recent study of 47 very low birth weight ventilator-dependent infants at 7 to 14 days of age also compared two levels of dosing, although the low dose used was greater than the low dose we used[30]. In that study, twenty-three infants were randomized to receive dexamethasone at 0.5 mg/kg/d intravenously for 3 days, 0.25 mg/kg/d for 3 days, and 0.1 mg/kg/d during the 7th day; 24 infants received low dose dexamethasone as 0.2 mg/kg/d for 3 days and 0.1 mg/kg/d for 4 days. The authors concluded that their low dose had comparable beneficial effects on dynamic pulmonary mechanics, oxygen requirement, and applied ventilatory support in very low birth weight infants compared to high dose dexamethasone[30] Similarly, our study, which used an even lower dose, showed comparable pulmonary effects between groups. Our high and low dose groups had similar proportion extubated during dexamethasone course, change in FiO_2 during dexamethasone course, ventilator days, hospital days, adjusted age at discharge, O_2 requirement at 36 weeks, need for chronic lung disease medications at discharge, and adjusted age at room air. Given the lack of placebo arm, we cannot know whether or not the effect on chronic lung disease is completely dependent on steroid treatment. Future steroid studies would benefit from a placebo arm in order to determine whether pulmonary improvement is a result of treatment or related to natural course of the disease.

For protection of human subjects, the study was closed before the intended number of infants could be enrolled. Nonetheless, differences existed between the groups' outcomes. Compared to the low dose group, the high dose group had significantly more infants who required treatment for hypertension. Infants in the high dose group had more abnormal neurodevelopmental outcomes at one year adjusted age. The high dose group also had more patients with hyperglycemia, slower weight gain during treatment, slower head growth during treatment, and a smaller mean head circumference at one year adjusted age, although these differences did not reach statistical significance. With such a small number of infants enrolled before recruitment was halted, the study may lack the power to detect differences in some outcome variables. Of note, two patients in the high dose group were withdrawn on day six of the seven day dexamethasone course secondary to adverse side effects. No patient in the low dose group experienced side effects that resulted in study withdrawal.

Given the concern regarding dexamethasone treatment of infants and its associated increased risk of short- and long-term complications, including impaired growth and neurodevelopmental delay, this study would have benefitted from a placebo arm. A comparison of the side effects of high dose dexamethasone, low dose dexamethasone, and "no dose" dexamethasone would have been useful. Although our study focused on short term adverse effects, the concern regarding dexamethasone safety mandates that new studies using low dose glucocorticoid therapy or physiologic replacement should include long-term follow-up of pulmonary and neurodevelopmental outcome. The risk of short- and long-term complications associated with dexamethasone limits its use in the clinical arena. Our data support the American Academy of Pediatrics and the Canadian Paediatric Society in their recommendation against high dose dexamethasone treatment.

NOTES

(1) "What is already known on this topic" - the dangers of using dexamethasone in infants with chronic lung disease.

(2) "What this study adds" - NICUs throughout North America are still using dexamethasone, although to a lesser degree. This study adds to the body of evidence illustrating the dangers of using administrating this drug to neonates.

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