

EARLY INHALED GLUCOCORTICOID THERAPY TO PREVENT BRONCHOPULMONARY DYSPLASIA

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ABSTRACT

Background The safety and efficacy of inhaled glucocorticoid therapy for asthma stimulated its use in infants to prevent bronchopulmonary dysplasia. We tested the hypothesis that early therapy with inhaled glucocorticoids would decrease the frequency of bronchopulmonary dysplasia in premature infants.

Methods We conducted a randomized, multicenter trial of inhaled beclomethasone or placebo in 253 infants, 3 to 14 days old, born before 33 weeks of gestation and weighing 1250 g or less at birth, who required ventilation therapy. Beclomethasone was delivered in a decreasing dosage, from 40 to 5 μ g per kilogram of body weight per day, for four weeks. The primary outcome measure was bronchopulmonary dysplasia at 28 days of age. Secondary outcomes included bronchopulmonary dysplasia at 36 weeks of postmenstrual age, the need for systemic glucocorticoid therapy, the need for bronchodilator therapy, the duration of respiratory support, and death.

Results One hundred twenty-three infants received beclomethasone, and 130 received placebo. The frequency of bronchopulmonary dysplasia was similar in the two groups: 43 percent in the beclomethasone group and 45 percent in the placebo group at 28 days of age, and 18 percent in the beclomethasone group and 20 percent in the placebo group at 36 weeks of postmenstrual age. At 28 days of age, fewer infants in the beclomethasone group than in the placebo group were receiving systemic glucocorticoid therapy (relative risk, 0.6; 95 percent confidence interval, 0.4 to 1.0) and mechanical ventilation (relative risk, 0.8; 95 percent confidence interval, 0.6 to 1.0).

Conclusions Early beclomethasone therapy did not prevent bronchopulmonary dysplasia but was associated with lower rates of use of systemic glucocorticoid therapy and mechanical ventilation. (N Engl J Med 1999;340:1005-10.)

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BRONCHOPULMONARY dysplasia is a chronic pulmonary disorder that occurs primarily in premature infants with respiratory insufficiency who require supplemental oxygen and ventilatory support. The pathogenesis of bronchopulmonary dysplasia is multifactorial and incompletely understood, but it involves acute and chronic lung injury accompanied by inflammation, fibrosis, and remodeling.¹ Prolonged ventilatory support and supplemental oxygen contribute to the lung injury and inflammation. Infants who have broncho-

pulmonary dysplasia or are at risk for the disorder are often treated with systemic glucocorticoids. A recent meta-analysis of systemic glucocorticoid therapy in premature infants within the first two weeks of life concluded that this therapy reduced the frequency of bronchopulmonary dysplasia.² Although there is evidence of short-term pulmonary improvement,²⁻⁸ there is no consensus about the early use of systemic glucocorticoid therapy, because of concern about its adverse effects on growth and on the development of the lungs and other organ systems.⁹

The primary impetus for the development of aerosolized glucocorticoid therapy was to reduce the need for systemic glucocorticoid therapy, with its attendant side effects in adults and children with inflammatory respiratory disease such as asthma. Inhaled glucocorticoid therapy has achieved this goal while providing effective antiasthma therapy.¹⁰⁻¹² Given its safety and efficacy in adults and children, inhaled glucocorticoid therapy has been increasingly used for the treatment of bronchopulmonary dysplasia in neonates.⁹ We designed a trial to test the hypothesis that early administration of glucocorticoid by inhalation to premature infants decreases the incidence of bronchopulmonary dysplasia and has few adverse effects.

METHODS

Study Subjects

The study was a randomized, double-blind, placebo-controlled, multicenter trial approved by the institutional review boards of the three participating centers. The study subjects were infants 3 to 14 days of age who were at increased risk for bronchopulmonary dysplasia because of their prematurity (a gestational age of less than 33 weeks and a birth weight of 1250 g or less) and need for mechanical ventilation. They were enrolled between October 1993 and April 1997. Informed consent was obtained from the infants' parents.

Infants were excluded if there was evidence of acute sepsis (according to clinical diagnosis or positive blood, cerebrospinal fluid, or urine culture), glucose intolerance (blood glucose concentration, >120 mg per deciliter [6.7 mmol per liter]), hypertension (systolic blood pressure, >100 mm Hg),¹³ necrotizing

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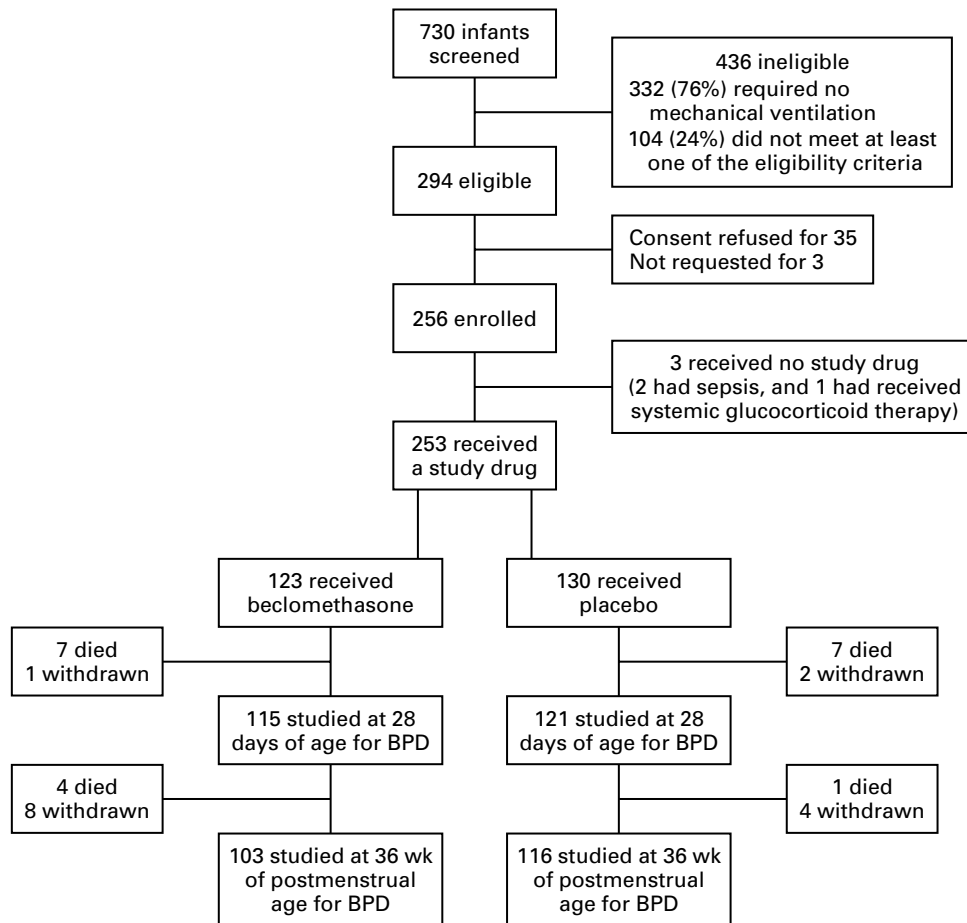


Figure 1. Summary of Infant Screening, Enrollment, and Analysis for Bronchopulmonary Dysplasia (BPD) at 28 Days of Age and 36 Weeks of Postmenstrual Age.

enterocolitis (according to physical and radiographic findings),¹⁴ abnormal renal function (a serum creatinine concentration of >2.1 mg per deciliter [$186 \mu\text{mol}$ per liter] and urine output of <0.3 ml per kilogram of body weight per hour for 24 hours), abnormal liver function (a serum alanine aminotransferase concentration of >108 U per liter or a serum aspartate aminotransferase concentration of >150 U per liter),¹⁵ major congenital abnormalities, or prior systemic glucocorticoid therapy.

The infants were stratified for randomization according to study site, sex, birth weight (≤ 900 g or >900 g), and severity of pulmonary disease (oxygenation index [the fraction of inspired oxygen times the mean airway pressure times 100, divided by the partial pressure of arterial oxygen], ≥ 5 or <5). The data coordinating center provided a randomization schedule to the pharmacy at each study center.

Study Protocol

Beclomethasone dipropionate (Beclvent, Allen and Hansbury, Glaxo Wellcome) and placebo metered-dose inhalers providing $42 \mu\text{g}$ per actuation were obtained from the drug manufacturer. Beclomethasone or placebo was delivered from the metered-dose inhaler with a valved holding chamber (Aerochamber, Monaghan Medical) interposed between a neonatal anesthesia bag and the infant's endotracheal tube. The delivery procedure was standardized with respect to ventilation technique and the actuation pro-

cedure for the metered-dose inhaler (5 breaths immediately after actuation at a rate of 40 breaths per minute; one minute between actuations, with a gas flow of 7 liters per minute; a peak inspiratory pressure of 15 to 20 mm Hg; and positive end-expiratory pressure of 5 mm Hg). For infants who no longer required mechanical ventilation during the treatment period, the study drug was administered by the same procedure through the endotracheal tube in the pharynx.

The protocol called for four weeks of treatment. The method of calculating the number of actuations delivered per day to each infant was identical for beclomethasone and placebo and was based on the desired dose of study drug to be delivered, the infant's weight, and the amount of study drug exiting the endotracheal tube: the desired dose (in micrograms per kilogram per day) times the weight (in kilograms) divided by the dose exiting the endotracheal tube (in micrograms per actuation) equaled the total number of actuations per day. The mean dose of beclomethasone exiting the endotracheal tube was $1.7 \mu\text{g}$ per actuation (4 percent per actuation dose), as measured in prior studies in vitro. The desired daily dose was calculated to deliver $40 \mu\text{g}$ per kilogram per day for the first week, 30 and $15 \mu\text{g}$ per kilogram per day during the second and third weeks, respectively, and 10 and then $5 \mu\text{g}$ per kilogram per day in the fourth week.

Systemic glucocorticoid therapy could be initiated at the discretion of the infant's attending physician if the infant had an

increasing oxygen requirement that was greater than the baseline requirement for at least five days and had received the study drug for a minimum of seven days. If systemic glucocorticoid therapy was initiated, treatment with the study drug was discontinued and the infant remained in the study for evaluation of outcomes.

Chest radiographs obtained at 28 days of age and 36 weeks of postmenstrual age were evaluated by a single radiologist who was unaware of the infants' study-group assignments. The radiographs were scored according to the system of Edwards,¹⁶ with a score of 3 or more considered abnormal. There was moderate reproducibility of the observer's interpretation of 16 randomly selected radiographs (mean [\pm SE] kappa value, 0.4 ± 0.2 ; $P = 0.03$).

Outcome Measures

The primary outcome measure was the frequency of bronchopulmonary dysplasia, as defined by an abnormal chest radiograph and dependence on supplemental oxygen at 28 days of life. A secondary outcome measure was bronchopulmonary dysplasia at 36 weeks of postmenstrual age, as defined by an abnormal chest radiograph and dependence on supplemental oxygen at that age. Other secondary end points were the duration of respiratory support (oxygen, mechanical ventilation, and continuous positive airway pressure); the need for systemic glucocorticoid, diuretic, or bronchodilator therapy; the frequency of air leak; and death. Other outcome measures included growth, blood pressure, blood glucose concentration, systemic infections and tracheal-aspirate colonization, length of hospitalization, clinical diagnoses of necrotizing enterocolitis, gastrointestinal hemorrhage, retinopathy of prematurity, cataracts, intracranial hemorrhage, and periventricular leukomalacia.

Statistical Analysis

We compared the study groups and outcome data with use of nonpaired t-tests for continuous variables and chi-square or Fisher's exact tests for categorical variables. We used nonparametric Wilcoxon rank-sum tests when the data were not normally distributed. We used a generalized estimation equation to analyze dichotomous outcome variables with repeated measures (e.g., bronchodilator and diuretic therapy) and mixed-model analysis for continuous outcome variables with repeated measures (e.g., blood pressure and blood glucose values). Analysis of variance was used to compare the changes in weight and length between groups. All statistical tests were two-sided.

The data and safety monitoring board requested one interim analysis after 125 infants had reached 28 days of age. According to the Lan-DeMets data-monitoring rule,¹⁷ there was no significant difference at this time ($P = 0.20$), and the study was therefore continued.

RESULTS

The numbers of infants who were screened and then participated in the study are shown in Figure 1. Three infants were excluded from the analysis because they had clinical sepsis (two infants) or began to receive systemic glucocorticoid therapy (one infant) before they had received any study drug. There was no significant difference in cumulative mortality between the groups at 28 days of age (6 percent in the beclomethasone group and 5 percent in the placebo group, $P = 0.92$) or through 36 weeks of postmenstrual age (9 percent in the beclomethasone group and 6 percent in the placebo group, $P = 0.40$). The numbers of infants remaining for analysis of bronchopulmonary dysplasia at 28 days of age and 36 weeks of postmenstrual age were

TABLE 1. BASE-LINE CHARACTERISTICS OF THE INFANTS IN THE BECLOMETHASONE AND PLACEBO GROUPS.*

CHARACTERISTIC	BECLOMETHASONE (N=123)	PLACEBO (N=130)
Birth weight (g)	800 \pm 193	802 \pm 189
Birth weight \leq 900 g (%)	71	70
Gestational age (wk)	26 \pm 2	26 \pm 2
Male sex (%)	51	53
Multiple gestation (%)	26	28
Mother's race or ethnic group (%)†		
White	41	54
Black	28	31
Asian	7	2
Hispanic	15	11
Other	9	2
Age at enrollment (days)	5.7 \pm 3.4	5.4 \pm 2.9
Any antenatal glucocorticoid exposure (%)	77	68
Oxygenation index at entry	3.7 \pm 3.1	4.1 \pm 3.8
Respiratory distress syndrome (%)	100	99
Surfactant therapy (%)	95	97

*Plus-minus values are means \pm SD.

† $P = 0.03$ for all racial and ethnic categories.

236 and 219, respectively. The base-line characteristics of the groups were similar, with the exception of maternal race or ethnic group (Table 1). The mean (\pm SD) age at enrollment was 5.7 ± 3.4 days for the beclomethasone group and 5.4 ± 2.9 days for the placebo group. One hundred twenty of the 123 infants in the beclomethasone group (98 percent) and 127 of the 130 infants in the placebo group (98 percent) were enrolled between three and seven days of age.

Seventy-one percent of the infants received at least 90 percent of their planned doses of the study drug. The reasons for receiving less than 90 percent of the planned dose were the initiation of systemic glucocorticoid therapy (55 infants), death or withdrawal from the study (14 infants), and other reasons (4 infants).

Respiratory Outcomes

The frequency of bronchopulmonary dysplasia at both 28 days of age and 36 weeks of postmenstrual age was similar in the two groups (Table 2). However, significantly fewer infants in the beclomethasone group were receiving systemic glucocorticoid therapy at 28 days of age (17 percent, as compared with 29 percent in the placebo group; $P = 0.03$) and at 36 weeks of postmenstrual age (36 percent, as compared with 48 percent in the placebo group; $P = 0.05$). The probability of receiving systemic glucocorticoid therapy between birth and 28 days of age was 51 percent lower in the beclomethasone group than in the placebo group after gestational age, antenatal glucocorticoid exposure, and the oxygena-

TABLE 2. OCCURRENCE OF BRONCHOPULMONARY DYSPLASIA, USE OF SYSTEMIC GLUCOCORTICOID THERAPY, AND NEED FOR MECHANICAL VENTILATION AT 28 DAYS OF AGE AND 36 WEEKS OF POSTMENSTRUAL AGE IN THE BECLOMETHASONE AND PLACEBO GROUPS.

OUTCOME	BECLOMETHASONE	PLACEBO	P VALUE*	RELATIVE RISK (95% CI)†
	no./total no. evaluated (%)			
At 28 days of age				
Bronchopulmonary dysplasia	50/115 (43)	55/121 (45)	0.76	1.0 (0.7–1.3)
Systemic glucocorticoid therapy	21/123 (17)	37/129 (29)	0.03	0.6 (0.4–1.0)
Mechanical ventilation	55/115 (48)	75/120 (62)	0.02	0.8 (0.6–1.0)
At 36 weeks of postmenstrual age				
Bronchopulmonary dysplasia	19/103 (18)	23/116 (20)	0.80	0.9 (0.5–1.6)
Systemic glucocorticoid therapy	44/123 (36)	62/129 (48)	0.05	0.7 (0.6–1.0)
Mechanical ventilation	6/104 (6)	11/118 (9)	0.32	0.6 (0.2–1.6)

*The chi-square test was used for statistical comparisons.

†CI denotes confidence interval.

tion index were controlled for (relative risk, 0.5; 95 percent confidence interval, 0.3 to 0.9) (Fig. 2).

Significantly fewer infants in the beclomethasone group than in the placebo group were receiving mechanical ventilation at 28 days of age, but the difference was not significant at 36 weeks of postmenstrual age (Table 2). The infants in the beclomethasone group tended to have fewer days of supplemental oxygen and mechanical ventilation and fewer days of hospitalization, but the differences were not statistically significant (Table 3). The infants in the beclomethasone group received significantly less bronchodilator therapy through 36 weeks of postmenstrual age (odds ratio, 0.6; 95 percent confidence interval, 0.4 to 1.0; $P=0.04$), but not less diuretic therapy (odds ratio, 0.8; 95 percent confidence interval, 0.6 to 1.1; $P=0.16$). The effects of beclomethasone

therapy on bronchopulmonary dysplasia and mortality did not differ with respect to birth weight or oxygenation index.

Other Clinical Outcomes

There was no difference between the two groups in the frequency of systemic infections or tracheal colonization with fungi or bacteria. In the placebo group, as compared with the beclomethasone group, the mean blood glucose concentration was higher; this difference was statistically, but not clinically, significant after adjustment for systemic glucocorticoid therapy. There was no significant difference between the groups in the mean systolic or diastolic blood pressure, the change in weight or length, or the frequency of retinopathy of prematurity, cataracts, intracranial hemorrhage, periventricular leukomalacia, necrotizing enterocolitis, or gastrointestinal bleeding, after adjustment for systemic glucocorticoid therapy (Table 4).

DISCUSSION

We found no difference in the incidence of bronchopulmonary dysplasia at 28 days of age or 36 weeks of postmenstrual age in premature infants treated with inhaled beclomethasone or placebo. However, beclomethasone therapy was associated with less need for systemic glucocorticoid and bronchodilator therapy, and fewer infants assigned to receive beclomethasone were receiving mechanical ventilation at 28 days of age. The increase in systemic glucocorticoid therapy in the placebo group probably diminished the differences between the groups in terms of bronchopulmonary dysplasia and other respiratory outcome measures. Had systemic glucocorticoid therapy not been permitted until after 28 days of age, the differences between study groups might have

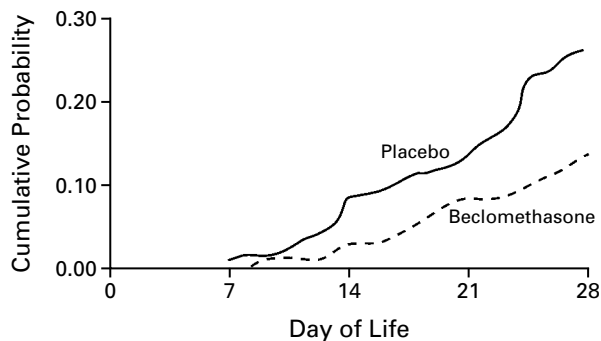


Figure 2. Probability of Receiving Systemic Glucocorticoid Therapy in the Beclomethasone and Placebo Groups during the First 28 Days of Life, According to Cox Regression Analysis with Control for Gestational Age, Antenatal Glucocorticoid Exposure, and the Oxygenation Index.

been larger. We think our decision to allow systemic glucocorticoid therapy in patients was clinically and ethically appropriate. We addressed the potential confounding influence of radiographic misclassification on our primary outcome measure by comparing study groups with respect to the proportion of infants receiving supplemental oxygen at 28 days of age and 36 weeks of postmenstrual age without radiographic criteria. No difference was found between the study groups.

In smaller trials of infants with established bronchopulmonary dysplasia, inhaled glucocorticoid therapy appeared to reduce the need for systemic glucocorticoid and bronchodilator therapy, improved acute pulmonary function, and facilitated weaning from mechanical ventilation and supplemental oxygen.¹⁸⁻²¹ These reports also suggested no apparent adverse effects of inhaled glucocorticoid therapy, although Linder et al.²² described hypertrophy of the tongue in three infants that was possibly related to inhaled glucocorticoid therapy lasting one to two months. The absence of short-term adverse effects in our trial is reassuring but is relevant only to the regimen we used. Kovacs et al.²³ found that infants receiving early systemic dexamethasone therapy for 3 days and then nebulized budesonide therapy for 18 days were less likely to need subsequent systemic glucocorticoid therapy than infants receiving placebo but had no reduction in bronchopulmonary dysplasia.

We chose to compare beclomethasone with placebo instead of systemic glucocorticoid therapy, because early systemic therapy was considered experimental and not standard care at the time this study was designed.

One limitation of inhalation studies, including this study, is the uncertainty of drug delivery and deposition in the lungs. Numerous factors affect aerosol delivery and deposition, including particle size, delivery devices and techniques, and the presence or absence of intubation.²⁴⁻³³ Estimates of delivered doses apply only to the technique, conditions, and system used. Although we achieved benefits in terms of some pulmonary outcomes, it is possible that bronchopulmonary dysplasia was not reduced because there was inadequate deposition of glucocorticoid in the lower respiratory tract. In animal studies and one study of human neonates, aerosol delivery was often less than 5 percent of the original aerosolized dose.^{24,25,31-33}

Our estimated dose delivered (tapered from 40 to 5 μg per kilogram per day) is high relative to the estimated inhaled dose in maintenance therapy for asthma in adults and children (0.5 to 3.2 μg per kilogram per day). The decision to administer the study drug through the endotracheal tube positioned in the pharynx of infants who no longer required mechanical ventilation before completion of

TABLE 3. DURATION OF SUPPLEMENTAL OXYGEN THERAPY, MECHANICAL VENTILATION, AND HOSPITALIZATION IN THE BECLOMETHASONE AND PLACEBO GROUPS.

OUTCOME	BECLOMETHASONE	PLACEBO	P VALUE*
	median no. of days (25th, 75th percentiles)		
Duration of supplemental oxygen therapy	62 (32, 88)	72 (45, 99)	0.11
Duration of mechanical ventilation	26 (15, 43)	37 (17, 48)	0.09
Length of hospitalization	92 (69, 113)	99 (73, 116)	0.19

*The Wilcoxon rank-sum test was used for group comparisons.

TABLE 4. OTHER CLINICAL OUTCOMES IN THE BECLOMETHASONE AND PLACEBO GROUPS.*

OUTCOME	BECLOMETHASONE	PLACEBO
Blood glucose — mg/dl†	93±2	98±2‡
Blood pressure — mm Hg		
Systolic	65±1	65±1
Diastolic	38±1	37±1
Growth from study day 1 to 29		
Weight — g	263±17	276±15
Length — cm	2.7±0.3	2.7±0.2
Retinopathy of prematurity — no. (%)	93 (76)	100 (77)
≤Stage 2	64	74
>Stage 2	29	26
Laser therapy	16	10
Cataracts	0	1
Intracranial hemorrhage — no. (%)	46 (37)	49 (38)
Grade 1 or 2	31	38
Grade 3 or 4	15	11
Periventricular leukomalacia — no. (%)	8 (7)	7 (5)
Necrotizing enterocolitis — no. (%)	15 (12)	26 (20)
Gastrointestinal bleeding — no. (%)	1 (1)	3 (2)

*Plus-minus values are means ±SE, adjusted for systemic glucocorticoid therapy.

†To convert values for glucose to millimoles per liter, multiply by 0.05551.

‡P=0.01.

the inhalation protocol was based on our in vitro results, which suggested that there was no measurable delivery of aerosol by face mask. Less beclomethasone deposition was expected with pharyngeal than with intratracheal delivery, but this adaptation appeared to optimize aerosol delivery in infants who had ceased to require mechanical ventilation.

We conclude that early inhaled glucocorticoid therapy in premature infants at risk for bronchopulmonary dysplasia is associated with a lower rate of subsequent therapy with systemic glucocorticoids and bronchodilators and a lower rate of mechanical ventilation at 28 days of age.

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