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Death or Neurodevelopmental Impairment at 18 To 22 Months in a Randomized Trial of Early Dexamethasone to Prevent Death or Chronic Lung Disease in Extremely Low Birth Weight Infants

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Abstract

Objective—To evaluate the incidence of death or neurodevelopmental impairment (NDI) at 18 to 22 months corrected age in subjects enrolled in a trial of early dexamethasone treatment to prevent death or chronic lung disease in extremely low birth weight infants.

Methods—Evaluation of infants at 18 to 22 months corrected age included anthropomorphic measurements, a standard neurological examination, and the Bayley Scales of Infant Development-II, including the Mental Developmental Index (MDI) and the Psychomotor Developmental Index (PDI). NDI was defined as moderate or severe cerebral palsy, MDI or PDI less than 70, blindness, or hearing impairment.

Results—Death or NDI at 18 to 22 months corrected age was similar in the dexamethasone and placebo groups (65 vs 66 percent, $p=0.99$ among those with known outcome). The proportion of survivors with NDI was also similar, as were mean values for weight, length, and head circumference and the proportion of infants with poor growth (50 vs 41 percent, $p=0.42$ for weight less than 10th percentile). Forty nine percent of infants in the placebo group received treatment with corticosteroid compared to 32% in the dexamethasone group ($p=0.02$).

Conclusion—The risk of death or NDI and rate of poor growth were high but similar in the dexamethasone and placebo groups. The lack of a discernible effect of early dexamethasone on neurodevelopmental outcome may be due to frequent clinical corticosteroid use in the placebo group.

Keywords

neurodevelopmental outcome; growth; bronchopulmonary dysplasia; cerebral palsy; neonatal follow-up

Introduction

Corticosteroid treatment before 8 days of age decreases the incidence of chronic lung disease (CLD) at 36 weeks postmenstrual age and facilitates weaning from mechanical ventilation (1). However, dexamethasone use is associated with serious short-term adverse effects and may increase the risk of neurodevelopmental impairment (NDI) (1,2,3).

We conducted a multicenter randomized trial of early dexamethasone treatment to prevent death or CLD in extremely low birth weight (ELBW) infants (4). Although we used a lower dose than in most previous trials, we observed frequent complications in the dexamethasone group, including a high rate of gastrointestinal perforation that resulted in early termination of the trial. We evaluated subjects enrolled in the trial at 18 to 22 months corrected age to

assess the effect of early dexamethasone treatment on death or NDI and on growth. Although this study was completed following the trial, we present this information because of the relative paucity of data on outcomes of infants with early postnatal exposure to glucocorticoids.

Methods

Description of original trial

A randomized, double-masked, placebo controlled trial was conducted in 13 centers of the NICHD Neonatal Research Network between February 1998 and September 1999 (4). The trial protocol, including the follow-up component, was approved by the Institutional Review Board at each site, and written informed consent was obtained from a parent of each infant.

Inclusion criteria were a birth weight of 501 to 1000 g, treatment with mechanical ventilation within 12 hours after birth, and the presence of an indwelling vascular catheter. Additional inclusion criteria for infants with birth weight greater than 750 g were supplementation with a fraction of inspired oxygen of 0.3 or more and the administration of at least one dose of surfactant. In a two-by-two factorial design, infants were randomly assigned to one of four groups according to study medication (dexamethasone or placebo) and ventilator management (routine treatment or permissive hypercapnia). Study medication was started within 24 hours after birth. The dexamethasone-treated groups received an initial dose of 0.15 mg per kg per day for three days; the dose was tapered over the next seven days (0.1 mg per kg per day for three days, 0.05 mg per kg per day for two days, and 0.02 mg per kg per day for two days). The placebo groups received equivalent volumes of saline. The protocol allowed use of open-label dexamethasone if required for clinical management, but this was discouraged during the ten-day study period.

The trial was stopped early because of an unanticipated and unacceptable rate of gastrointestinal perforations in the dexamethasone group. Because the effect of dexamethasone treatment did not vary according to ventilator management, the two dexamethasone groups and two placebo groups were combined for analysis.

A total of 220 infants were enrolled; 111 received dexamethasone and 109 received placebo. Death or CLD (defined as the use of oxygen supplementation at 36 weeks postmenstrual age) was comparable (relative risk = 0.92, (95 percent confidence interval, 0.76 to 1.11). Weight and head circumference at 36 weeks postmenstrual age were significantly less in the dexamethasone group.

Follow-up evaluation

Parents of surviving infants were encouraged to participate in a comprehensive follow-up evaluation at 18 to 22 months corrected age (5). Contact was maintained with the families by interim visits, telephone, and/or letter, and an appointment was scheduled for the assessment.

The comprehensive neurodevelopmental evaluation included an interview with the primary care taker of the infant, assessments of mental and motor development with the Bayley

Scales of Infant Development II, a neurologic examination, and ascertainment of hearing and vision impairment. Bayley Scale score of <70 (> 2 SD below the mean) in either the Mental Developmental Index (MDI) or Psychomotor Developmental Index (PDI) was considered to indicate significant delay. Neurologic examination was based on the Amiel-Tison method (6); the examination was considered abnormal if abnormalities were identified in tone, strength, reflexes, angles, or posture. Cerebral palsy was defined as a non-progressive disorder characterized by abnormal tone in 1 extremity and abnormal control of movement and posture. Cerebral palsy was further classified as mild (impairment interfered only slightly with age-appropriate motor activities), moderate (no ambulation or ambulation only with assistive devices but can sit independently or with support), and severe (no ambulation or supported sitting). Blindness was defined as no useful vision in either eye. Deafness was defined as disability with bilateral hearing amplification. NDI, a composite measure, was defined as one or more of the following: moderate or severe cerebral palsy, MDI or PDI < 70 , blindness, or deafness. Examiners whose reliability was established prior to the study and verified in subsequent videotapes of infant examinations performed both the neurologic and developmental assessments. Examiners were masked to treatment assignment.

Statistical Analysis

Baseline data and treatment group differences for infants who have known and unknown primary outcome (death or NDI) were compared by t-tests for continuous data and chi-square tests for categorical data. Fisher's exact test was used for categorical outcomes with frequency counts less than six. Logistic regression analysis was used to analyze differences in neurodevelopmental findings, growth, and medical complications between treatment groups. Analyses were adjusted for center, birth weight (501-750 g; 751-1000 g), ventilator management group, and sex. For the outcome variables with sparse data, center was deleted from the logistic regression models in order to satisfy the convergence criteria of the models. For continuous outcomes, generalized least squares models were used.

Results

Death or NDI, the primary outcome, was known in 102 (92 percent) infants in the dexamethasone group and 92 (84 percent) in the placebo group (Table 1). Of the 220 infants enrolled in the trial, 164 infants were available for follow-up at 18 to 22 months corrected age. A total of 144 infants were seen (76 in the dexamethasone group, 68 in the placebo group), which comprised 88 percent of surviving infants, a rate similar for both groups. No MDI or PDI was recorded in 6 infants in the placebo group, so that NDI was calculated for only 62 infants, accounting for the reduced number with known outcome in that group.

Baseline sociodemographic characteristics of the mothers of all infants enrolled were similar between groups. Of those evaluated at follow-up, the majority of mothers were 19 years old or more (84%) and unmarried (58%). Of the infants, 92 percent lived with their biologic mother. Annual income was less than \$20,000 in 47% and 62% received Medicaid. The racial distribution was 51 percent black, 40 percent white, 7 percent Hispanic, and 2 percent other and was not different between groups. English was the primary language in 92% and

Spanish in 6%. Baseline perinatal variables of the infants, including birth weight, gestational age, small for gestational age status, and sex were similar between treatment groups (Table 2). Among the infants seen at follow-up, 5 infants treated with early dexamethasone and 3 who received placebo had spontaneous gastrointestinal perforations during their hospital course. Fewer infants in the dexamethasone group received subsequent clinical treatment with corticosteroid (32 versus 49 percent, $p = 0.02$ among those with known outcome). Other neonatal outcomes, including CLD, intraventricular hemorrhage, periventricular leukomalacia, and retinopathy of prematurity were similar. Infants with outcome known were similar to those with outcome not known, except for clinical steroid use.

The mean corrected age at the time of follow-up evaluation was 20 ± 2.5 (SD) months for both the dexamethasone and placebo groups. Among the infants with known primary outcome, the proportion with death or NDI was similar in both groups (relative risk = 1.02 [95% CI = 0.84-1.23]) (Table 3). Six infants (8 percent) in the dexamethasone group and 8 infants (12 percent) in the placebo group were diagnosed with moderate to severe cerebral palsy. Of those, four in each group had quadriplegia; two in the dexamethasone group and four in the placebo group had diplegia. Nine additional infants had mild cerebral palsy, 5 in the dexamethasone and 4 in the placebo group. Mean MDI and PDI and the proportion of children in each group with MDI and PDI less than 70 were similar in both groups, as was the proportion of infants with an abnormal neurological examination. Among the 6 infants with no calculated NDI, one had mild cerebral palsy and none had blindness or hearing impairment. In a secondary analysis of infants in the placebo group, although the primary outcome was similar, surviving infants exposed to clinical steroid treatment tended to have worse outcomes (Table 4).

Medical outcomes were similar in both groups although the 95% confidence intervals do not exclude clinically important differences (Table 5, online). Following the first hospital discharge, 58 and 59 percent of the infants in the dexamethasone and placebo groups, respectively, required at least one additional hospital admission, and 37 and 38 percent, respectively, received medications, such as diuretics or bronchodilators, to treat pulmonary disorders. Five infants in the dexamethasone group and four in the placebo group were receiving supplemental oxygen at the time of the visit.

Mean values for weight, length, and head circumference were similar in the dexamethasone and placebo groups (Table 6, online). The proportions of infants in both groups with measurements less than the tenth percentile for weight, length, and head circumference (7) were also comparable, although the 95% confidence intervals did not exclude clinically important differences.

Discussion

With the sample size evaluated in this trial, we detected no discernable difference between treatment assignments in death or NDI at 18 to 22 months corrected age. Our results differ from those of three randomized trials in which dexamethasone treatment using a higher dose and/or longer duration was associated with an increased incidence of neurological abnormality (8-11). Other trials of postnatal dexamethasone beginning either early in the

first week (12-14) or at 7 or more days (15-18) did not show conclusive detrimental effects on neurodevelopmental outcome, similar to ours. However, all of these trials were smaller than our trial and thus more susceptible to type II error. Furthermore, although other trials have used low doses of dexamethasone (16,18), ours is the first to investigate the long-term effects of an early lower dose.

The likelihood of an adverse effect of dexamethasone on brain development is supported by studies in animals and humans. Pharmacological doses of glucocorticoids administered to neonatal animals during critical periods of brain development may impair brain cell division and differentiation, myelination, and electrophysiological reactions, and cause delayed behavioral changes (19,20,21). In preterm infants treated with dexamethasone for CLD, cerebral cortical gray matter volume measured with quantitative magnetic resonance imaging was reduced by 35 percent, compared to untreated infants (22).

The absence of a discernable effect on neurodevelopmental outcome may be due to our use of a lower dose and shorter duration of dexamethasone treatment than in many trials. The initial dose we used was approximately equivalent to five times the estimated physiologic cortisol secretion rate (23), in contrast to the higher doses typically used in trials and clinical practice at the time our study was conducted. However, this dose resulted in short term adverse effects, such as hypertension and hyperglycemia, similar to those observed with higher doses (1,2). The limited pharmacokinetic data available indicate that the half-life of dexamethasone is prolonged in ELBW infants compared to children and adults (24,25). Accumulation of the drug may have contributed to high levels of dexamethasone that increased the rate of early adverse effects.

Another explanation for the lack of a detectable difference in outcome between treatment groups is the frequent clinical use of dexamethasone (4). As observed in other trials of early dexamethasone treatment (26,27), clinical corticosteroid use was greater in the placebo than the dexamethasone group. This open-label use may have obscured any effects of early dexamethasone on neurodevelopmental outcome in the entire group. In addition, it is possible that dexamethasone may not increase the incidence of adverse neurologic outcomes in populations with the highest baseline risk of chronic lung disease (28). However, our secondary analysis of infants in the placebo group suggests poorer outcomes in those given open-label steroid treatment and is concerning, although the small sample size limits a definitive conclusion.

Our study is one of the largest studies reporting long-term outcome and the largest reporting long-term outcome for this relatively low early dexamethasone dose (8-18). We intended to enroll a sufficient number of infants to test whether early lower dose dexamethasone treatment reduced death or CLD, our primary outcome, and to exclude a clinically significant increase in cerebral palsy at 18 to 22 months corrected age. However, the trial was stopped early because of the increased rate of gastrointestinal perforation in the dexamethasone group. Nevertheless, the importance of long-term neurodevelopmental evaluation in subjects who have participated in trials of postnatal corticosteroids is well recognized (3). Furthermore, dexamethasone remains in clinical use for infants at high risk

of CLD because of its beneficial pulmonary effects, underscoring the need for as much unbiased data as feasible regarding its long-term effects.

We observed a small but significant decrease in weight and head circumference at 36 postmenstrual weeks in the dexamethasone group compared to placebo, despite substantial clinical corticosteroid use in both groups. This difference was not sustained at 18 to 22 months, perhaps indicating greater catch-up growth in the dexamethasone-treated infants. However, a substantial rate of growth impairment was observed in the entire cohort. This likely reflects poor postnatal growth in hospitalized very low birth weight infants, especially those with severe illness (29), which may limit later catch-up growth (30).

Meta-analyses of trials of dexamethasone treatment initiated before 8 days and after 7 days show a decrease in CLD at 36 weeks postmenstrual age and more successful weaning from mechanical ventilation (1,2). However, dexamethasone administration does not affect the length of hospitalization or mortality. In addition, treatment results in many short-term adverse effects, although serious adverse events such as gastrointestinal perforation are largely observed with early use. Although not demonstrated in our study, in a systematic review of early postnatal dexamethasone, treatment appears to increase the incidence of cerebral palsy and neurodevelopmental impairment (1). Given the serious short-term adverse effects not offset by discernable long-term benefit, the available evidence does not support the routine use of postnatal dexamethasone, particularly early use, to prevent death or CLD in ELBW infants. Whether subgroups of infants, such as those at extremely high baseline risk for CLD (28), would benefit or whether the use of late low-dose dexamethasone (18) or other glucocorticoids such as hydrocortisone would improve outcome remain to be established in appropriate clinical trials.

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List of Abbreviations

NDI	Neurodevelopmental impairment
MDI	Mental Developmental Index
PDI	Psychomotor Developmental Index
CLD	Chronic lung disease
ELBW	Extremely low birthweight

Table 1
Outcome assessment among enrolled infants

	Dexamethasone	Placebo
Enrolled in trial – no.	111	109
Died before discharge – no.	23	28
Died after discharge – no.	3	2
Available for follow-up – no.	85	79
Seen at follow-up- no. (%) of available	76 (89)	68 (86)
Primary outcome known – no. (%) of enrolled	102 (92)	92 (84)*

* No MDI or PDI was recorded for 6 infants in the placebo group so that NDI was available for 62 infants .

Table 2
Characteristics of the infants with outcome known and not known according to treatment assignment*

Variable	Outcome Known		Outcome not known		Comparison	
	Dex	Placebo	p ¹	Dex	Placebo	p ¹
	n = 102	n = 92		n = 9	n = 17	P-value ²
Baseline variables						
Birth weight – g.	733±132	724±129	0.66	756±128	795±145	0.50
Gestational age – wk.	25±1.75	25±1.64	0.95	25±1	26±1	0.63
Male – no. (%)	54(53)	49(53)	0.97	5(56)	6(35)	0.42
Inborn – no. (%)	95(93)	87(95)	0.68	9(100)	16(94)	1.00
SGA – no. (%)	12(12)	13(14)	0.62	1(11)	0(0)	0.35
Antenatal steroids – no. (%)	75(74)	70(76)	0.68	7(78)	12(71)	1.00
Neonatal Outcomes**						
BPD – no./total no. (%)	39/78(50)	41/66(62)	0.15	5(56)	12(71)	0.67
Clinical steroid use – no. (%)	33(32)	45(49)	0.02	5(56)	11(65)	0.69
IVH						
Any – no./total no. (%)	42/101(42)	28(30)	0.11	2(22)	9(53)	0.22
Severe (III or IV) – no./total no. (%)	21/101(21)	17(19)	0.69	1(11)	5(29)	0.38
PVL – no./total no. (%)	6/101(6)	6(7)	1.00	0(0)	1(6)	1.00
GI perforations – no. (%)	14(14)	7(8)	0.17	2(22)	1(6)	0.27
ROP (all grades) – no./total no. (%)	67/80(84)	53/64(83)	0.88	6/8(75)	13/16(81)	1.00

* Plus-minus values are means ± SD.

** Total number refers to the number of infants assessed for the outcome if different from the number in that group.

Dex = dexamethasone; SGA = small for gestational age; CLD = chronic lung disease, defined as oxygen supplementation at 36 weeks postmenstrual age; IVH = intraventricular hemorrhage; PVL = periventricular leukomalacia; GI perforation = spontaneous gastrointestinal perforation within first 14 days; ROP = retinopathy of prematurity.

¹ Comparison between dexamethasone and placebo groups with either known or unknown outcome.

² Comparison between infants with known and unknown outcomes.

Table 3
Mortality and neurodevelopmental findings at 18 to 22 months according to treatment assignment (adjusted analysis)

Variable	Dexamethasone No. / total No. (%)	Placebo No. / total No. (%)	RR (95% CI)	P-value
Primary outcome				
Death or NDI	66/102(65)	61/92(66)	1.00(0.83,1.21)	0.99
Specific outcomes in survivors				
Moderate to severe cerebral palsy	6/76(8)	8/68(12)	0.68(0.25,1.81)	0.43
Bilateral blindness	1/76(1.3)	0/67(0)	-	-
Deafness *	2/75(2.7)	2/67(3.0)	0.82(0.10,6.86)	0.86
Bayley MDI <70 *	35/76(46)	25/62(40)	1.11(0.76,1.62)	0.60
Bayley PDI <70	21/74(28)	22/62(35)	0.79(0.49,1.28)	0.34
NDI	40/76(53)	31/62(50)	0.99(0.72,1.36)	0.97
Abnormal neurologic exam *	20/76(26)	17/68(25)	1.02(0.59,1.78)	0.94

NDI = Neurodevelopmental impairment (moderate/severe cerebral palsy, MDI or PDI less than 70, blindness or hearing impairment). MDI = Mental developmental index; PDI = Psychomotor developmental index; RR is the relative risk of the outcome in the dexamethasone group as compared with the placebo group. CI denotes confidence interval.

* Not adjusted for center because of convergence issues.

Table 4
Mortality and neurodevelopmental findings at 18 to 22 months in infants assigned to placebo group according to subsequent clinical steroid use (adjusted analysis)

Variable	Placebo Steroid No. / total No. (%)	Placebo No Steroid No. / total No. (%)	RR (95% CI)	p-value
Primary outcome				
Death or NDI	31/45(69)	30/47(64)	0.85(0.64,1.13)	0.27
Specific outcomes in survivors				
Moderate to severe cerebral palsy	7/39(18)	1/29(3)	2.58(0.20,33.2)	0.47
Bayley MDI <70	15/34(44)	10/28(36)	1.12(0.55,2.27)	0.75
Bayley PDI <70	16/34(47)	6/28(21)	1.78(0.70,4.50)	0.22
NDI	20/34(59)	11/28(39)	1.22(0.65,2.31)	0.53
Abnormal neurologic exam	16/39(41)	1/29(3)	11.02(1.21,100.33)	0.03

NDI = Neurodevelopmental impairment (moderate/severe cerebral palsy, MDI or PDI less than 70, blindness or hearing impairment). MDI = Mental developmental index; PDI = Psychomotor developmental index; RR is the relative risk of the outcome in the placebo group treated with steroid as compared with the placebo group that did not receive steroid. CI denotes confidence interval. Not adjusted for center due to convergence issues.

Table 5
Medical complications at follow-up according to treatment assignment (adjusted analysis)

Variable	Dexamethasone No. / total No. (%)	Placebo No. / total No. (%)	RR (95% CI)	P-value
Re-hospitalization*	44/76(58)	40/68(59)	0.96(0.74,1.26)	0.77
Pulmonary medications	28/76(37)	26/68(38)	0.95(0.65,1.39)	0.84
Oxygen use at follow-up*	5/74(7)	4/67(6)	1.09(0.29,4.07)	0.79

RR is the relative risk of the outcome in the dexamethasone group as compared with the Placebo group. CI denotes confidence interval.

* Not adjusted for center because of convergence issues.

Table 6
Growth at 18 to 22 months according to treatment assignment (adjusted analysis)

Variable	Dexamethasone n=76	Placebo n=68	RR (95% CI)	P-value
Male – no. (%)	38(50)	33(49)		0.86
Clinical steroid use – no. (%)	28(37)	39(57)		0.01
Growth parameters	Mean ± S.D			
Weight – kg.	10.3±1.6	10.3±1.4		0.98
Length – cm.	80.3±4.9	80.0±4.2		0.60
Head circumference - cm	46.8±2.2	46.6±2.1 **		0.59
Growth < 10th percentile				
Weight – no. (%)	38(50)	27(40)	1.16(0.81,1.66)	0.42
Length - no. (%) *	19(25)	21(31)	0.76(0.45,1.27)	0.29
Head circumference – no. (%) *	21(28)	19(28) **	0.96(0.57,1.63)	0.88

RR is the relative risk of the outcome in the dexamethasone group as compared with the placebo group. CI denotes confidence interval.

* Not adjusted for center because of convergence issues.

** In the placebo group, n=67 for head circumference