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

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Objective To evaluate the incidence of death or neurodevelopmental impairment (NDI) at 18-22 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.

Study design Evaluation of infants at 18-22 months corrected age included anthropomorphic measurements, a standard neurological examination, and the Bayley Scales of Infant Development-II, including the Mental Developmental Index and the Psychomotor Developmental Index. NDI was defined as moderate or severe cerebral palsy, Mental Developmental Index or Psychomotor Developmental Index <70, blindness, or hearing impairment.

Results Death or NDI at 18-22 months corrected age was similar in the dexamethasone and placebo groups (65% vs 66%, $P = .99$ 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%, $P = .42$ for weight less than 10th percentile); 49% of infants in the placebo group received treatment with corticosteroid compared with 32% in the dexamethasone group ($P = .02$).

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. *(J Pediatr 2014;164:34-9)*.

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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).[1-3]

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 (GI) perforation that resulted in early termination of the trial. We evaluated

CLD	Chronic lung disease
ELBW	Extremely low birth weight
GI	Gastrointestinal
MDI	Mental Developmental Index
NDI	Neurodevelopmental impairment
PDI	Psychomotor Developmental Index

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subjects enrolled in the trial at 18-22 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 National Institute of Child Health and Human Development 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 501-1000 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 >750 g were supplementation with a fraction of inspired oxygen of 0.3 or more and the administration of at least 1 dose of surfactant. In a 2-by-2 factorial design, infants were randomly assigned to 1 of 4 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 3 days; the dose was tapered over the next 7 days (0.1 mg per kg per day for 3 days, 0.05 mg per kg per day for 2 days, and 0.02 mg per kg per day for 2 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 GI perforations in the dexamethasone group. Because the effect of dexamethasone treatment did not vary according to ventilator management, the 2 dexamethasone groups and 2 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% CI, 0.76-1.11]. 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 18-22 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 caretaker 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 nonprogressive 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 Analyses

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 χ^2 tests for categorical data. Fisher exact test was used for categorical outcomes with frequency counts <6. 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%) infants in the dexamethasone group and 92 (84%) in the placebo group (Table I). Of the 220 infants enrolled in the trial, 164 infants were available for follow-up at 18-22 months corrected age. A total of 144 infants were seen (76 in the dexamethasone group, 68 in the placebo group), which comprised 88% 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