

Controlled Trial of Early Dexamethasone Treatment for the Prevention of Chronic Lung Disease in Preterm Infants: A 3-Year Follow-up

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ABSTRACT. *Objective.* There is increasing concern in regard to the possible long-term adverse effects of postnatal dexamethasone treatment in preterm infants. The purpose of this study was to assess growth and neurodevelopmental outcome in preterm infants at high risk of chronic lung disease (CLD), treated with early (<96 hours) postnatal dexamethasone.

Design. Three-year follow-up data of physical growth and neurodevelopmental outcome of preterm infants enrolled in a controlled trial to study the effectiveness of early postnatal dexamethasone administration for the prevention of CLD were reviewed. The original trial included 25 treated neonates who received dexamethasone intravenously from the fourth day of life for 7 days (0.5 mg/kg/d for the first 3 days, 0.25 mg/kg/d the next 3 days, and 0.125 mg/kg/d on the seventh day), and 25 untreated neonates as controls. Forty-five surviving infants (22 untreated and 23 treated) completed the 3-year follow-up.

Results. At the end of follow-up, infants pertaining to both study groups had similar values for body weight, height, and head circumference, and a similar incidence of infants with anthropometrics data below the third percentile. Moreover, no differences were detected between the groups in regard to incidence of major cranial ultrasound abnormalities, cerebral palsy, major neurosensory impairment or IQ scores, and distribution.

Conclusions. Early (<96 hours) postnatal dexamethasone administration at the doses employed in this study did not impair physical or neurodevelopmental outcome in preterm infants at high risk of CLD. However, the small sample size of our study was not tailored to look for long-term outcomes and our results are not in agreement with those of larger trials and systematic reviews. The real risks of postnatal dexamethasone administration could be definitely assessed only when more well-designed trials using long-term neurodevelopmental assessment as the primary outcome will be reported. *Pediatrics* 2002;109(6). URL: <http://www.pediatrics.org/cgi/content/full/109/6/e85>; *chronic lung disease, postnatal dexamethasone, follow-up, preterm infants, neurodevelopmental outcome.*

ABBREVIATIONS. CLD, chronic lung disease; SD, standard deviation; CI, confidence interval; OR, odds ratio; PHH, posthemorrhagic hydrocephalus.

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Early postnatal dexamethasone administration has been successfully used for the prevention of chronic lung disease (CLD) in preterm infants.¹ Short-term adverse effects during dexamethasone treatment have been widely reported, and during the late 1990s some reports of serious long-term sequelae appeared. The few published studies²⁻⁴ and a recent systematic review of randomized, controlled trials⁵ suggested the possibility of a dexamethasone-induced risk of cerebral palsy and neurodevelopmental impairment. This risk of neurologic impairment is consistent with the observation of a reduction of cortical gray matter volume in preterm infants receiving postnatal dexamethasone.⁶

We recently conducted a clinical trial on the use of early postnatal dexamethasone administration in preterm infants at high risk of CLD,⁷ and the present report summarizes the findings at follow-up at 3-year postnatal adjusted age.

METHODS

Brief Description of Original Study

This was a randomized, unblinded clinical trial⁷ that was performed to study the effects of early postnatal dexamethasone in the prevention of CLD during a 2-year period ending in October 1998. The Ethical Committee of the Department of Pediatrics approved the study protocol, and informed consent from the parents was obtained. Inclusion criteria was as follows: birth weight <1250 g, gestational age <32 weeks, ventilator- and oxygen-dependent at 72 hours of life, and high risk of CLD according to our scoring system. This score is based on gestational age, birth weight, respiratory distress syndrome, grade of respiratory support (in term of peak inspiratory pressure and inspired oxygen concentration), and some major neonatal complications (pulmonary interstitial emphysema, patent ductus arteriosus, intraventricular hemorrhage > grade 2, sepsis). A previous study indicated that >90% of infants fulfilling these inclusion criteria would develop CLD at 28 days of life.⁸ Using the sample-size table with the 90% CLD incidence in the control group and an expected 60% reduction in the treated group, at least 20 infants in each group were required to detect a difference, allowing a 5% chance of α type I error. The randomization, obtained by random number allocation, was revealed when numbered, sealed envelopes were opened and was conducted at 72 hours of life. Infants with prenatal infections, congenital malformations, and evidence of sepsis at randomization were excluded from the study.

Fifty infants were enrolled and randomly assigned after 72 hours of life to the dexamethasone group (25) or the control group (25). The treated infants received dexamethasone intravenously from the fourth day of life for 7 days (0.5 mg/kg/d the first 3 days, 0.25 mg/kg/d for the next 3 days, and 0.125 mg/kg/d on the seventh day). No steroid treatment was administered to the control group during the study period. Both study groups were well-matched for all the clinical variables, and there were no differences between groups in the incidence for major morbidity, as reported at discharge from the unit (Table 1). The results of this

TABLE 1. Baseline Characteristics, Major Morbidity, and Survival

	Dexamethasone Group (<i>n</i> = 25)	Control Group (<i>n</i> = 25)
Gestational age, wk	28.2 (25–31)	28.4 (25–30)
Birth weight, g	940 (590–1250)	940 (610–1250)
Sex ratio (M/F)	14/11	13/12
Antenatal steroids	13 (52)	11 (44)
Patent ductus arteriosus	13 (52)	17 (68)
Intraventricular hemorrhage >grade 2	5 (20)	6 (24)
Periventricular leucomalacia	2 (8)	2 (8)
Septicemia	8 (32)	7 (28)
Necrotizing enterocolitis	2 (8)	3 (12)
Retinopathy of prematurity >grade 2	9 (36)	8 (32)
Survivors at 28 d	25 (100)	25 (100)
Survivors at discharge	23 (92)	22 (88)
CLD at 28 d	11 (44)*	24 (96)*
Ventilated at 28 d	4 (16)†	13 (52)†
Oxygen therapy at 36 wk	3:23 (13)‡	17:23 (73.9)‡

Values expressed as median (range) or number (percent).

* $P = .0001$; OR 0.336 (95% CI: 0.202–0.559).

† $P < .02$; OR 0.175 (95% CI: 0.046–0.662).

‡ $P < .0001$; OR 0.052 (95% CI: 0.011–0.244).

study have been previously reported.⁷ In summary, the incidence of CLD at 28 days of life and at 36 weeks' postconceptional age was significantly lower in the dexamethasone group as compared with the control group. Hyperglycemia, hypertension, growth failure, and mainly left ventricle hypertrophy were the transient adverse effects associated with early steroid administration. A single dose of 0.5 mg/kg of dexamethasone was administered to 3 infants in the dexamethasone group and to 13 infants in the control group who were still ventilated after the 28th day of life to facilitate extubation. Among retreated infants, 3 control infants and 2 treated infants died and were not included in the follow-up.

Follow-up Study

Forty-five infants (22 controls and 23 treated) surviving at discharge were enrolled in the follow-up to 34 to 42 months of adjusted postnatal age. The follow-up controls were performed by the same pediatrician (R.L.) with periodic visits at 3, 8, 12, 24, 36, and 42 months of adjusted age. All visits and tests were performed in the presence of the infant's parents (mother and/or father). At each visit, an interim medical history was associated with a physical examination. Weight, supine crown-heel length, and occipitofrontal head circumference measurements were recorded, and anthropometric measurements were plotted on the growth chart for Italian children.

On visits at 3, 8, and 12 months of corrected age, a cranial ultrasound scan was performed. Major cranial ultrasound abnormality were defined, according to the work of Stewart and colleagues, as 1) subependymal/intraventricular hemorrhage with posthemorrhagic hydrocephalus requiring placement of a shunt; 2) persistent but non progressive ventricular dilatation; 3) intraparenchymal echodensity or echolucency in the periventricular white matter (consistent with periventricular hemorrhagic infarction or periventricular leukomalacia).⁹ All infants underwent a neurologic examination by a pediatric neurologist (G.T.) to assess motor development. Neuromotor dysfunction was classified as mild, moderate, or severe, based on the mobility of the child: mild if motor dysfunction was not sufficiently severe to interfere with mobility, moderate if the child was independently mobile when hand-holding was provided, and severe when the child was not independent.¹⁰ Psychometric evaluations were performed at 24 and 36 months of age using the Stanford-Binet Scale of Intelligence (third revised version by Terman-Merrill).¹¹ Children were subdivided into 3 groups according to the IQ score: 1) IQ <70; 2) IQ 70 to 90; 3) IQ >90. Behavioral abnormalities include eating, sleeping, and anxiety problems. The examiners, both the pediatrician and the pediatric neurologist, were completely blinded to group assignment. For analysis of physical growth and developmental performance, the infant's postnatal age was corrected by the degree of prematurity before term (40 weeks).

Differences in outcomes were analyzed using Fisher exact test for categorical variables or the Mann Whitney *U* test for continuous variables. A P value <.05 was considered significant.

RESULTS

The mean (\pm standard deviation [SD]) corrected postnatal age at the time of follow-up was 35.3 (\pm 4.1) months for the early dexamethasone group and 35.2 (\pm 3.4) months for the control group. Respiratory follow-up of studied infants was obtained from parents during the interim medical history associated with each follow-up examination. On the basis of such information, 6 treated infants had severe repeated respiratory illness (pneumonia, bronchitis, and asthma) versus 14 control infants, and this difference is statistically significant ($P < .02$) with an odds ratio (OR) of 0.201 and 95% confidence interval (CI): 0.056 to 0.720. The incidence of rehospitalization was 43.5% (10/23) in the dexamethasone group and 68.2% (15/22) in the control group, but the difference is not statistically significant. Three infants of the control group required repeated rehospitalization because of occurrences of lower respiratory tract infection (bronchiolitis, pneumonia, asthma). Two infants of the treated group and 4 control infants required surgical intervention for inguinal hernia; all infants with posthemorrhagic hydrocephalus (PHH) required neurosurgery for shunt revision, and 1 infant in each group needed ocular surgery to remove scleral buckling.

Table 2 reports the growth outcome for the studied infants. There was no significant difference between the study groups in regard to mean (\pm SD) body weight (11.8 \pm 1.6 vs 12.0 \pm 1.8 kg), height (88.9 \pm 4.8 vs 91.1 \pm 4.3 cm), and head circumference (48.6 \pm 1.6 vs 48.7 \pm 2.0 cm). Body weight, height, and circumference of the head were plotted, based on the corrected age, on the growth chart for Italian children. The incidence of infants with body weight, height or head circumference within normal range (3rd–97th percentile) according to corrected age was similar in both study groups. Three infants in the treated group and 4 infants in the control group had body weight below the third percentile. Two infants in each group had height below the third percentile, whereas 3

TABLE 2. Growth Outcome

	Early Dexamethasone Group (n = 23)	Control Group (n = 22)	OR or Difference Between Means (95% CI)
Age at follow-up (mo)	35.7 ± 4.1 (34–42)	35.6 ± 3.4 (34–42)	0.10 (–2.371–2.171)
Body weight (Kg)	11.84 ± 1.62 (9.15–15.60)	12.00 ± 1.82 (9.25–15.80)	–0.17 (–0.865–1.205)
Below 3rd percentile	3 (13)	4 (18.2)	0.675 (0.132–3.435)
3rd–97th percentile	20 (86.9)	17 (77.3)	1.961 (0.407–9.434)
Above 97th percentile	0	1 (4.5)	0.305 (0.011–7.900)
Body height (cm)	89.9 ± 4.8 (79.3–103.5)	91.1 ± 4.3 (80.5–104)	–1.2 (–1.546–3.946)
Below 3rd percentile	2 (8.7)	2 (9.1)	0.952 (0.122–7.427)
3rd–97th percentile	21 (91.3)	20 (90.9)	1.050 (0.134–8.188)
Above 97th percentile	0	0	
Head circumference (cm)	48.6 ± 1.6 (44.5–50.2)	48.7 ± 2.0 (44.9–51.9)	–0.10 (–0.987–1.187)
Below 3rd percentile	3 (13)	3 (13.6)	0.950 (0.170–5.303)
3rd–97th percentile	20 (86.9)	19 (86.4)	1.053 (0.188–5.876)
Above 97th percentile	0	0	

Data presented as mean ± SD (range) or number (%).

infants of each group had head circumference below the third percentile.

Neurodevelopmental outcome data are reported in Table 3. At 12 months of corrected age, 5 infants of the treated group (21.7%) and 6 of control group (27.3%) showed major cranial ultrasound abnormalities diagnosed as PHH, persistent ventricular dilatation or periventricular leukomalacia, giving an OR of 0.740 (95% CI: 0.189–2.900). Cerebral palsy was diagnosed in 2 treated (8.7%) and 3 control infants (13.6%), giving an OR of 0.603 (95% CI: 0.090–4.010), and all of them were subjects with major cranial ultrasound abnormalities. Among treated infants, spastic quadriplegia was associated with PHH, whereas spastic hemiplegia and ataxia were associated with persistent ventricular dilatation. The 2 cases of spastic quadriplegia observed in the control group were associated with persistent ventricular dilatation or PHH. Major neurosensory impairment was observed in 3 treated (13%) and 5 control infants (22.7%), giving an OR of 0.510 (95% CI: 0.106–2.454). Two treated infants and 1 control became blind because of retinal detachment after cryosurgery for severe retinopathy of prematurity; cerebral palsy, PHH, and mental retardation were also associated in

these infants. Two control infants had severe deafness: in 1 infant it was associated with mental retardation and persistent ventricular dilatation, whereas in the other one it was attributable to antibiotics toxicity. Moderate hearing loss was diagnosed in 1 treated infant and in 2 control infants. The mean (± SD) IQ score was 85.8 ± 13.9 for the treated group and 85.6 ± 16.3 for the control group. Eleven treated infants and 12 control infants had IQ scores of >90, whereas the IQ scores were <70 for 3 infants in each study group. Three treated (13%) and 5 control (22.7%) infants showed behavioral abnormalities (eating, sleeping, and anxiety problems), giving an OR of 0.510 (95% CI: 0.106–2.454).

DISCUSSION

Several studies have reported short-term benefits with postnatal steroid treatment in the prevention or treatment of CLD of prematurity.^{1,12} Although short-term adverse effects such as hyperglycemia, hypertension, growth impairment, cardiac hypertrophy, gastrointestinal bleeding and perforation, sepsis, and periventricular leukomalacia have been reported,^{12–15} few published trials have been designed to evaluate the long-term follow-up of treated infants.

TABLE 3. Neurodevelopmental Outcome

	Early Dexamethasone Group (n = 23)	Control Group (n = 22)	OR or Difference Between Means (95% CI)
Major cranial ultrasound abnormalities at 12 mo of corrected age	5 (21.7)	6 (27.3)	0.740 (0.189–2.900)
Periventricular leukomalacia	1 (4.3)	1 (4.5)	0.954 (0.055–16.28)
Persistent ventricular dilatation	4 (17.4)	5 (22.7)	0.715 (0.164–3.110)
PHH	2 (8.7)	2 (9.1)	0.952 (0.122–7.427)
Cerebral palsy	2 (8.7)	3 (13.6)	0.603 (0.090–4.010)
Spastic quadriplegia	1 (4.3)	2 (9.1)	0.454 (0.038–5.408)
Spastic hemiplegia	1 (4.3)	0	3.00 (0.115–77.71)
Ataxia	0	1 (4.5)	0.305 (0.011–7.900)
Major neurosensory impairment	3 (13)	5 (22.7)	0.510 (0.106–2.454)
Blindness	2 (8.7)	1 (4.5)	2.00 (0.168–23.79)
Poor vision	0	0	
Severe deafness	0	2 (9.1)	0.183 (0.008–4.033)
Moderate hearing loss	1 (4.3)	2 (9.1)	0.454 (0.038–5.408)
IQ score	85.8 ± 13.9 (60–104)	85.6 ± 16.3 (50–110)	0.20 (–9.29–8.89)
>90	11 (47.8)	11 (50)	0.916 (0.284–2.953)
70–90	9 (39.1)	8 (36.4)	1.125 (0.336–3.761)
<70	3 (13)	3 (13.6)	0.950 (0.170–5.303)
Behavior abnormalities	3 (13)	5 (22.7)	0.510 (0.106–2.454)

Data presented as mean ± SD (range) or number (%).

Recent reports have underlined concerns regarding postnatal steroids that may cause neurodevelopmental impairment in preterm infants.^{2–5,16} Thus, alarm and censure against postnatal steroid administration in preterm infants arrives from all directions.^{16–20} This has been further fomented by the data obtained by Murphy et al,⁶ who reported an important impairment in brain growth, principally affecting cerebral gray matter, secondary to systemic dexamethasone therapy. It is now claimed that neonates who received postnatal steroids in randomized, controlled studies should have detailed neurologic follow-up to assess the real risk/benefit ratio of such therapy.²¹

Our experience reports the findings of a 3-year follow-up in premature infants included in a randomized, clinical trial for early postnatal dexamethasone administration. The follow-up data on the infants included in this study failed to demonstrate a negative effect attributable to the treatment on physical growth and neurodevelopmental outcome at 3 years' corrected age. At the end of follow-up, the infants of both study groups showed similar values for body weight, height, and head circumference, and a similar incidence of anthropometrics data below the third percentile. Furthermore, no difference was detected between the groups in regard to the incidence of major cranial ultrasound abnormalities, cerebral palsy, major neurosensory impairment and IQ scores, and distribution.

Available data dealing with the real risk of long-term adverse effects of postnatal steroid therapy in preterm infants are not univocal. In fact, the studies of Mammel,²² Cummings,²³ O'Shea,²⁴ Jones,²⁵ and Ferrara²⁶ reported similar outcomes for treated and untreated infants, while in 1998 Yeh et al² documented a higher incidence of neuromotor dysfunction in dexamethasone-treated infants and O'Shea et al,³ in 1999 reported an increased risk of cerebral palsy. However, several possible limitations in many of these studies should be mentioned: differences in confounding factors between study groups;^{3,23} contamination of randomization schedules;² small study population, and short duration of follow-up.^{22,24,26} A major problem regards differences in doses and duration of dexamethasone administration, as well as in the postnatal age at the start of treatment. In particular, those studies reporting a higher incidence of neuromotor dysfunction and increased risk of cerebral palsy^{2,3} included infants treated with high doses of dexamethasone and for lengthy periods of time (28 days from the first day of life² and 42 days from the third week after birth³). It is noteworthy, however, that Shinwell et al⁴ recently reported follow-up data obtained at mean (SD) age of 53¹⁸ months on infants included in a randomized, double-blind, placebo-controlled study, conducted in 18 neonatal intensive care unit in Israel using a 3-day course of early postnatal dexamethasone. They concluded that even such a short course of dexamethasone is associated with a significant increase of cerebral palsy (OR: 4.62; 95% CI: 2.38–8.98) and developmental delay (OR: 2.87; 95% CI: 1.53–5.38). Notwithstanding the numerous limitations of their study (children not

examined by a single investigator, absence of data on chorioamnionitis, administration of steroids after age 7 day for treatment of CLD, high percentage of subjects without valid data of follow-up [16.4%], and the minimum age of 24 months at which reliable follow-up data were obtained) the authors offer a word of caution, because 22% of the children with cerebral palsy had normal cranial ultrasound, and all were treated with dexamethasone.

In our trial, the study groups were well-matched in respect to all clinical data with the exception of the incidence of CLD, duration of mechanical ventilation, and duration of oxygen therapy. Treated infants received a total dexamethasone dose of 2.375 mg/kg administered over 7 days starting from the fourth day of life, and our results were probably not influenced by contamination of randomization, because the use of dexamethasone therapy after the study period was limited to 1 dose of 0.5 mg/kg to facilitate extubation in 1 treated infant and in 10 control infants. Our follow-up results with this schedule show no detrimental effects associated with dexamethasone therapy on long-term growth and neurodevelopmental outcome. However, a major limitation of our study could be the small size of the sample: in fact, the sample size was calculated on the basis of the incidence of CLD in our high-risk population to detect the reduction of CLD in treated infants and thus probably insufficiently powered to detect an association between dexamethasone and adverse long-term outcome.

The alarm regarding possible detrimental effects attributable to postnatal steroids on brain growth and developmental outcome should not be ignored. Postnatal steroid therapy seems currently to be so widespread as to exceed, in some countries, antenatal steroid treatment^{27,28} while its use should be carefully evaluated on a cost-benefit basis. However, we cannot agree with Barrington¹⁶ who emphasizes the need to abandon postnatal steroid therapy in preterm infants. It seems more correct to follow the recent recommendation coming from the American Academy of Pediatrics and Canadian Paediatric Society,²⁹ who recently stated that postnatal use of systemic dexamethasone for the prevention or treatment of CLD should be limited to carefully designed randomized, double-masked controlled trials, and that the primary outcome of these trials should be survival without long-term developmental impairments. The identification of the most effective and safe schedule to be used in those infants at high risk of severe CLD could lead us to use postnatal steroid administration as an advisable and well-aimed rocket rather than a misguided one.

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