

ORIGINAL ARTICLE

Outcomes at School Age after Postnatal Dexamethasone Therapy for Lung Disease of Prematurity

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ABSTRACT

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BACKGROUND

We studied the outcomes at school age in children who had participated in a double-blind, placebo-controlled trial of early postnatal dexamethasone therapy (initiated within 12 hours after birth) for the prevention of chronic lung disease of prematurity.

METHODS

Of the 262 children included in the initial study, 159 lived to school age. Of these children, 146 (72 in the dexamethasone group and 74 in the control group) were included in our study. All the infants had had severe respiratory distress syndrome requiring mechanical ventilation shortly after birth. In the dexamethasone group, 0.25 mg of dexamethasone per kilogram of body weight was given intravenously every 12 hours for one week, and then the dose was tapered. We evaluated the children's growth, neurologic and motor function, cognition, and school performance.

RESULTS

Children in the dexamethasone group were significantly shorter than the controls ($P=0.03$ for boys, $P=0.01$ for girls, and $P=0.03$ for all children) and had a significantly smaller head circumference ($P=0.04$). Children in the dexamethasone group had significantly poorer motor skills ($P<0.001$), motor coordination ($P<0.001$), and visual-motor integration ($P=0.02$). As compared with the controls, children in the dexamethasone group also had significantly lower full IQ scores (mean $[\pm SD]$, 78.2 ± 15.0 vs. 84.4 ± 12.6 ; $P=0.008$), verbal IQ scores (84.1 ± 13.2 vs. 88.4 ± 11.8 , $P=0.04$), and performance IQ scores (76.5 ± 14.6 vs. 84.5 ± 12.7 , $P=0.001$). The frequency of clinically significant disabilities was higher among children in the dexamethasone group than among controls (28 of 72 [39 percent] vs. 16 of 74 [22 percent], $P=0.04$).

CONCLUSIONS

Early postnatal dexamethasone therapy should not be recommended for the routine prevention or treatment of chronic lung disease, because it leads to substantial adverse effects on neuromotor and cognitive function at school age.

POSTNATAL DEXAMETHASONE THERAPY has been used to treat or prevent chronic lung disease of prematurity¹⁻⁸; however, the long-term effects of dexamethasone on development are not known. We previously reported results from our two-year follow-up study of dexamethasone treatment⁹ and from other studies conducted in young children.¹⁰⁻²¹ These studies indicated that early postnatal dexamethasone therapy might affect somatic growth and neurodevelopmental outcome. Since the results of two-year follow-up cannot always predict future morbidity, there is a compelling need for long-term follow-up. In the current study, we analyzed the outcomes in the same cohort of children at school age.

METHODS

INITIAL STUDY

All infants born between October 1992 and April 1995 in six participating hospitals who had a birth weight between 500 and 1999 g and had severe respiratory distress syndrome requiring mechanical ventilation within six hours after birth were included in the initial double-blind, placebo-controlled clinical trial. In the dexamethasone group, dexamethasone sodium phosphate was administered intravenously every 12 hours, at a dose of 0.25 mg per kilogram of body weight from day 1 through day 7, 0.12 mg per kilogram from day 8 through day 14, 0.05 mg per kilogram from day 15 through day 21, and 0.02 mg per kilogram from day 22 through day 28. The first dose was given within 12 hours after birth. The study was approved by the scientific and human experimentation committee of each hospital. Written informed consent was obtained from the parents in each case.

A total of 262 infants were included in the initial study; 130 received saline placebo, and 132 received dexamethasone. During the study, none of the physicians or caretakers were aware of the treatment assignments. The results of the study have been reported previously.¹ In summary, early dexamethasone therapy significantly reduced the incidence of chronic lung disease diagnosed either at 28 days after birth (21 of 132 in the dexamethasone group [16 percent] vs. 40 of 130 in the control group [31 percent], $P=0.004$) or at 36 weeks after conception (20 of 132 [15 percent] vs. 37 of 130 [28 percent], $P=0.009$). The mortality rate was similar in the two groups (44 of 132 [33 percent] vs. 39 of 130 [30 percent], $P=0.56$).

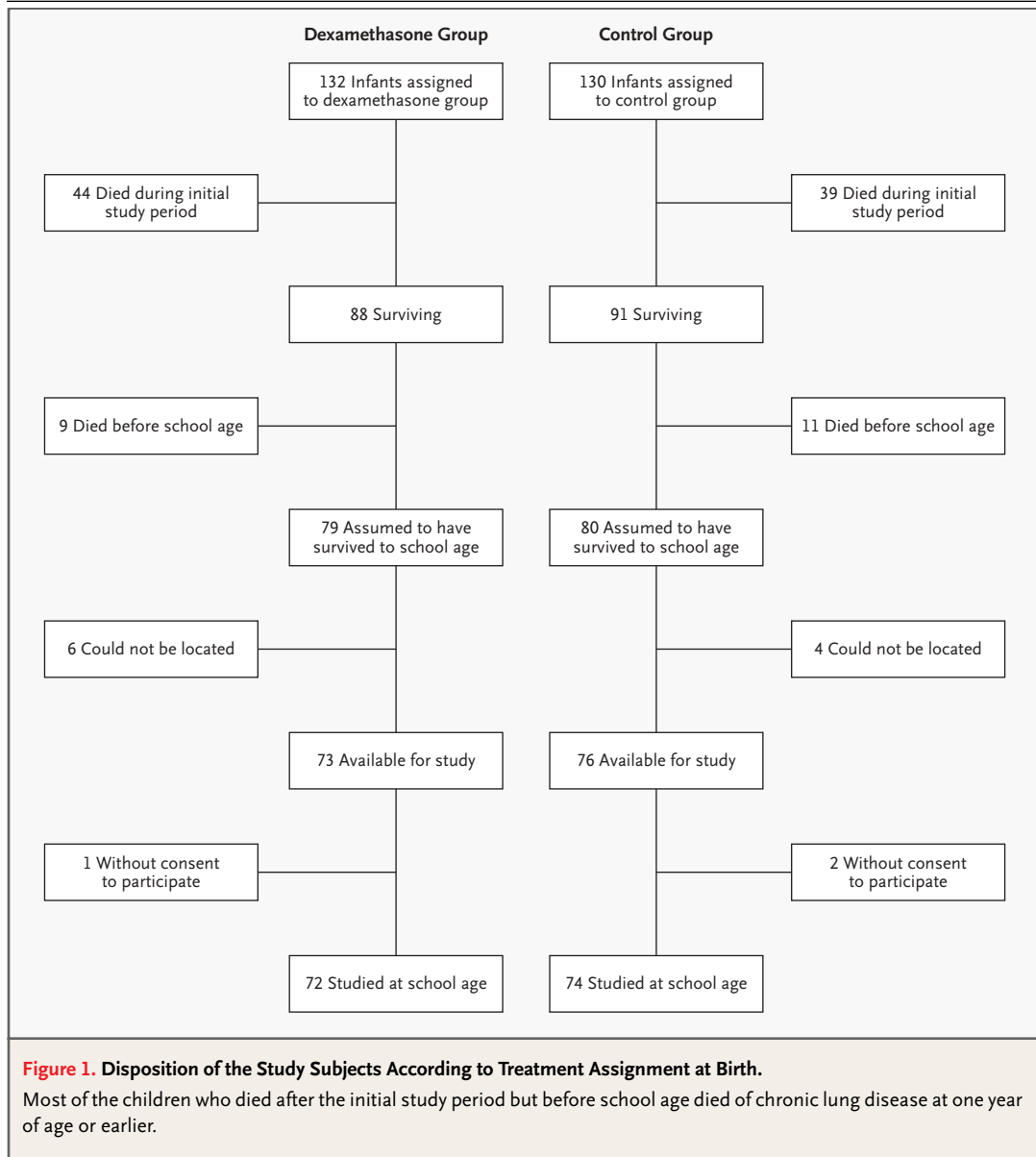
Clinical suspicion of sepsis was slightly, but not significantly, more common in the dexamethasone group than in the control group (30 of 132 [23 percent] vs. 19 of 130 [15 percent], $P=0.09$). Bacteremia was identified in 13 infants in the dexamethasone group (10 percent) and 8 infants in the control group (6 percent). The total number of infants with bacteremia, clinical sepsis, or both was significantly higher in the dexamethasone group than in the control group (43 of 132 [33 percent] vs. 27 of 130 [21 percent], $P=0.03$). Meningitis occurred in four infants in each group. Fungus cultures were available in three participating hospitals. Four infants in the control group and four in the dexamethasone group had fungemia (*Candida albicans*). Transient hyperglycemia, hypertension, cardiac hypertrophy, hyperparathyroidism, and a transient delay in weight gain were associated with dexamethasone therapy. An initial follow-up study at two years of age showed that the dexamethasone-treated children had poorer somatic growth and neuromuscular function than the children in the control group.⁹

FOLLOW-UP STUDY

Of the 262 children included in the initial study, 159 lived to school age. Of these children, 146 (92 percent) were included in the current study (72 in the dexamethasone group and 74 in the control group). Figure 1 indicates what happened to the children in each group up to the time of the current study.

A follow-up evaluation team was formed. None of the team members were aware of the study design or the clinical courses of the children. At the visit, an interim medical history was obtained and a physical examination was performed. The head circumference was measured, with the use of a tape measure, from the superior borders of the eyebrows anteriorly to the occipital protuberance posteriorly. The weight and height were measured with the use of an electronic scale.

Neurologic examination was performed by a pediatric neurologist. A standard motor test, the Movement Assessment Battery for Children designed by Henderson and Sugden,²² was administered by a physical therapist. The test includes eight tasks, grouped under three headings: manual dexterity (which includes placing pegs, threading lace, and following a flower trail with a pencil on paper), ball skills (which include one-hand bounce and catch and throwing a beanbag into a box), and static and dynamic balance (which includes "stork balance" on one foot, jumping in squares, and heel-to-



toe walking). For each task the child was given a score, ranging from 0 to 5, depending on his or her age and performance; lower scores indicated better performance. The total impairment score was the sum of the scores on the eight tasks and ranged from 0 to 40.

Motor coordination, visual perception, and visual-motor integration were assessed by means of the Beery-Buktenica developmental test, fourth edition.²³ This test evaluated the success or failure of the drawing, the identification, or both the drawing and identification of a total of 27 geometric figures;

the total score ranges from 0 to 27, with higher scores indicating better performance. The performance score for each child was adjusted for age.

Cognitive function was assessed by means of the Wechsler Intelligence Scale for Children, third edition (WISC-III), with scales for full IQ, verbal IQ, and performance IQ. In addition, other composite cognitive outcomes measured by subscales of the WISC-III were assessed. All these tests have Chinese-language versions that have been verified by the Chinese Behavioral Science Association.

Hearing was measured with pure-tone audio-

metric screening. Hearing impairment was defined as a hearing loss of more than 20 dB in at least one ear. Visual acuity was tested with a Snellen chart. Visual impairment was defined as visual acuity of less than 20/60 in at least one eye.

Each child's academic performance was assessed by a teacher who had 20 years of experience in a special school for handicapped children. Arithmetic,²⁴ language,²⁵ and adaptive behavior²⁶ were evaluated. A parent, usually the mother, was interviewed with the use of questionnaires in order to characterize the child's adaptive behavior and performance in school. These questionnaires, which were modified from Kaufman and Kaufman²⁷ and Luckasson et al.,²⁸ assessed the personal and social proficiency of the child by measuring four domains: communication, daily living, socialization, and motor function.

The definition of clinically significant disability in this study was modified from the criteria of Robertson et al.²⁹ Any one of the following was defined as a clinically significant disability: a clinical diagnosis of cerebral palsy, visual acuity of less than 20/60, cognitive delay (a full IQ below the 5th percentile for age), and hearing impairment severe enough to require a hearing aid.

STATISTICAL ANALYSIS

Data were analyzed with the use of SAS software (SAS Institute). Analysis of variance and, when appropriate, t-tests were used to compare the groups in terms of continuous variables. Categorical variables were compared by means of the chi-square test. The correlation of two continuous variables was evaluated by means of simple two-variable regression analysis. Multiple correlations were performed to evaluate the outcomes at school age in relation to perinatal and neonatal factors. Results are expressed as means ±SD.

RESULTS

PERINATAL DATA AND SOCIOECONOMIC BACKGROUND

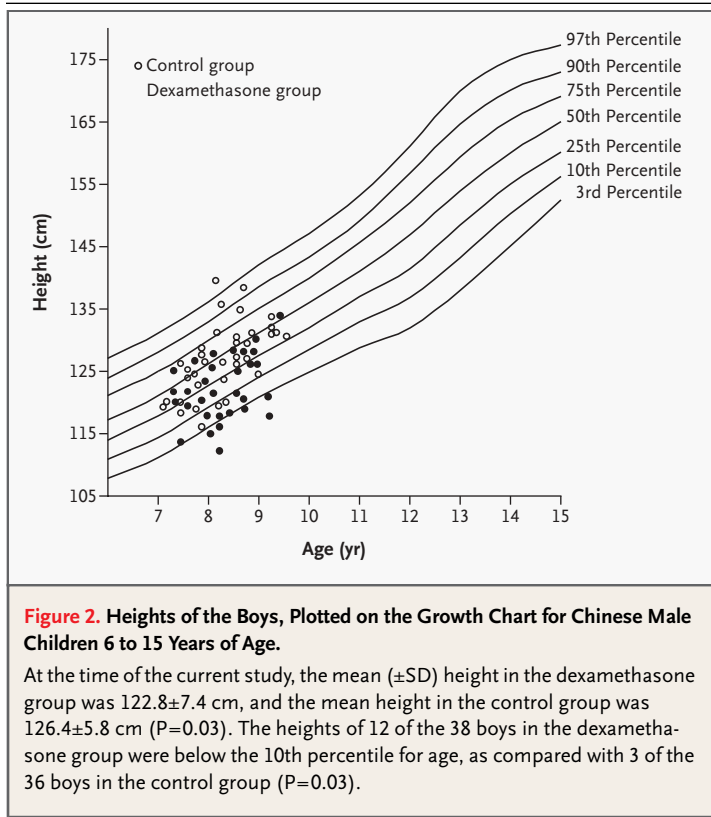
Perinatal and neonatal data and information about maternal education and socioeconomic background are summarized in Table 1. There were no significant differences between the groups in terms of these characteristics. The mean postnatal age at the time of the administration of the first dose of dexamethasone was 8.4±3.0 hours. The majority of the study population came from middle-class families,

Table 1. Perinatal Data and Socioeconomic Background.*

Characteristic	Dexamethasone Group (N=72)	Control Group (N=74)
Perinatal clinical characteristics		
Gestational age at birth (wk)	29.8±2.3	29.4±2.5
Birth weight (g)	1398±340	1371±343
Head circumference (cm)	27.8±2.0	27.5±2.5
Length (cm)	40.0±3.9	39.4±4.1
Sex (no.)		
Male	38	36
Female	34	38
Size for gestational age (no.)		
Appropriate	54	59
Small	18	15
Prenatal glucocorticoid therapy (no.)	22	24
Mode of delivery (no.)		
Caesarean	40	37
Vaginal	32	37
Apgar score		
At 1 min		
≤3	18	19
4–6	33	33
>6	21	22
At 5 min		
≤3	2	4
4–6	16	23
>6	54	47
Characteristics on admission to the trial		
Age at entry (hr)	8.4±3.0	8.1±3.0
Mean airway pressure (cm of water)	8.3±3.1	8.1±4.0
Fraction of inspired oxygen	0.67±0.30	0.65±0.25
Partial pressure of oxygen (mm Hg)	98±47	101±41
Partial pressure of carbon dioxide (mm Hg)	43±11	46±16
pH	7.30±0.09	7.29±0.10
Hematocrit (%)	44.2±6.8	43.5±7.2
Maternal characteristics		
Age (yr)	27.2±5.8	26.9±4.5
Level of education (no.)		
<12 yr	23	26
High-school graduation	36	37
College attendance	8	6
College graduation	5	5
Annual family income (no.)†		
<\$10,000	10	9
\$10,000–\$15,000	30	31
\$15,001–\$30,000	23	24
\$30,001–\$50,000	7	7
>\$50,000	2	3
Marital status (no.)		
Married	69	70
Single	0	0
Divorced	3	4

* Plus-minus values are means ±SD.

† Income is given in U.S. dollars.



and most mothers were high-school graduates (having ≥ 12 years of education).

NEONATAL COURSE

Of the children included in the long-term follow-up study, 15 in the dexamethasone group (21 percent) and 26 in the control group (35 percent) had chronic lung disease at the beginning of the study ($P=0.08$ for the comparison between groups). Children in the dexamethasone group required high-concentration oxygen therapy (concentration, >40 percent) for a shorter length of time than did controls (8.0 \pm 4.1 vs. 9.4 \pm 3.9 days, $P=0.04$). The two groups were similar in terms of the frequency of intraventricular hemorrhage (any intraventricular hemorrhage, 8 of 72 [11 percent] vs. 10 of 74 [14 percent]; intraventricular hemorrhage of grade 2 or worse, 3 of 72 [4 percent] vs. 2 of 74 [3 percent]), retinopathy of prematurity (15 of 72 [21 percent] vs. 11 of 74 [15 percent], $P=0.35$), and infection (clinical suspicion of sepsis, bacteremia, or both: 14 of 72 [19 percent] vs. 8 of 74 [11 percent], $P=0.22$; bacteremia: 6 of 72 [8 percent] vs. 3 of 74 [4 percent], $P=0.32$; meningitis: 1 of 72 [1 percent] vs.

1 of 74 [1 percent]). Six infants in the dexamethasone group (8 percent) and seven in the control group (9 percent) who had severe chronic lung disease required open-label glucocorticoid therapy after the completion of the initial study. Such therapy (0.25 mg per kilogram every 12 hours) was usually given for three to five days at the discretion of the individual attending physician to infants who were dependent on a respirator in order to facilitate extubation. Because of the relatively short duration of therapy, these infants were included in the analyses as members of their initially assigned groups.

GENERAL HEALTH AND PHYSICAL GROWTH

The mean age at the time of follow-up was 8.3 \pm 0.9 years among children in the dexamethasone group and 8.1 \pm 0.8 years among children in the control group. The two groups were similar in terms of the frequency of upper respiratory infection during the year when follow-up assessments were conducted (6 \pm 6 episodes per year in the dexamethasone group vs. 6 \pm 5 episodes per year in the control group) and in terms of blood pressure (systolic, 106 \pm 8 mm Hg vs. 108 \pm 8 mm Hg; diastolic, 59 \pm 8 mm Hg vs. 61 \pm 7 mm Hg).

The mean head circumference in the dexamethasone group (49.8 \pm 2.6 cm) was significantly smaller than that in the control group (50.6 \pm 2.1 cm, $P=0.04$). There was no significant difference in body weight between the dexamethasone group and the control group, either among boys or among girls (23.8 \pm 6.1 kg vs. 24.5 \pm 5.2 kg among boys, $P=0.59$; 23.0 \pm 3.2 kg vs. 24.4 \pm 5.7 kg among girls, $P=0.21$), but the mean height in the dexamethasone group was significantly lower than that in the control group (122.8 \pm 7.4 cm vs. 126.4 \pm 5.8 cm among boys, $P=0.03$; 121.3 \pm 5.4 cm vs. 124.7 \pm 5.6 cm among girls, $P=0.01$) (Fig. 2 and 3). Among both boys and girls, a significantly greater proportion of children in the dexamethasone group than in the control group had a height below the 10th percentile for their age group (Fig. 2 and 3).

NEUROLOGIC EXAMINATION AND ASSESSMENT OF MOTOR AND AUDIOVISUAL FUNCTION

The results of the neurologic examination were categorized as normal, borderline (defined as a delay in fine and gross motor skills or minor abnormalities in muscle tone), or abnormal (defined as the presence of cerebral palsy). The frequency of borderline or abnormal results tended to be higher in the dexamethasone group than in the control group,

although the difference was not statistically significant (20 of 72 [28 percent] vs. 14 of 74 [19 percent], $P=0.21$) (Table 2).

The dexamethasone group had significantly higher scores for manual dexterity, ball skills, balance, and total impairment than the control group, indicating that the motor performance in the dexamethasone group was poorer than that of controls (Table 2). A significantly greater proportion of children in the dexamethasone group than in the control group had motor-performance scores below the 5th percentile for their age group (29 of 72 [40 percent] vs. 15 of 74 [20 percent], $P=0.01$). Such a performance usually indicates a definite motor problem and a need for additional medical help.

Children in the dexamethasone group had poorer motor coordination, visual perception, and visual-motor integration than children in the control group (Table 2). There was no significant difference between the groups in the frequency of visual and hearing impairment (Table 2).

COGNITIVE FUNCTION

Children in the dexamethasone group had significantly lower full IQ, verbal IQ, and performance IQ scores and had significantly lower scores for perceptual organization, freedom from distractibility, and processing speed (Table 3).

SCHOOL PERFORMANCE

Seven children in the dexamethasone group and eight in the control group attended a special school for handicapped children. Children in the dexamethasone group had significantly lower scores on tests of arithmetic, phonetic transcription and perception, and grammar than those in the control group (Table 3). There was no significant difference between the groups on other language tests or in terms of various forms of adaptive behavior.

FREQUENCY OF DISABILITY

A significantly greater proportion of children in the dexamethasone group than in the control group had a clinically significant disability (Fig. 4).

CORRELATION OF DISABILITY WITH PERINATAL EVENTS

Within each group, there was no significant difference in perinatal characteristics or neonatal course, including the rate of prenatal glucocorticoid therapy and the Apgar score, between infants with clinically significant disability and those without such disability.

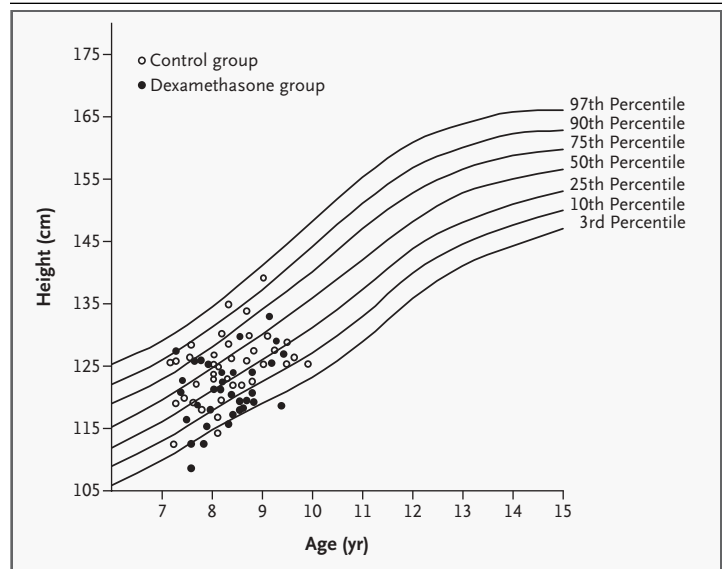


Figure 3. Heights of the Girls, Plotted on the Growth Chart for Chinese Female Children 6 to 15 Years of Age.

At the time of the current study, the mean (\pm SD) height in the dexamethasone group was 121.3 ± 5.4 cm, and the mean height in the control group was 124.7 ± 5.6 cm ($P=0.01$). The heights of 13 of the 34 girls in the dexamethasone group were below the 10th percentile for age, as compared with 4 of the 38 girls in the control group ($P=0.01$).

ity. However, there were significant correlations between the presence of clinically significant disability at school age and the severity of the early respiratory distress syndrome ($P=0.02$).

DISCUSSION

The present report summarizes the data from a group of school-age children who had participated in a placebo-controlled, double-blind trial of dexamethasone therapy begun within 12 hours after birth for the prevention of chronic lung disease.¹ Children who received early dexamethasone therapy (0.25 mg per kilogram every 12 hours) for one week, with a tapering of the dose over the course of the next three weeks, were more likely to have delays in somatic growth, impaired neuromotor and cognitive function, and disability at school age.

Glucocorticoids have been used for years to treat preterm infants who have or are at risk for chronic lung disease.¹⁻⁸ These agents often have the short-term benefits of improving lung compliance and facilitating early weaning from mechanical ventilation. In the past 20 years, dexamethasone has been given at various postnatal ages for a variety of rea-

Table 2. Results of Neurologic and Neuromotor Assessments and Audiovisual Function.*

Variable	Dexamethasone Group (N=72)	Control Group (N=74)	P Value
Neurologic examination (no. of children)			
Normal	52	60	NS
Borderline	3	5	NS
Abnormal (cerebral palsy)	17	9	NS
Movement Assessment Battery for Children score			
Manual dexterity	6.6±3.9	4.8±4.3	0.009
Ball skills	4.8±4.2	3.2±2.8	0.008
Balance	6.9±5.7	3.9±3.8	<0.001
Total impairment	19.2±12.4	11.6±10.3	<0.001
Visual-motor performance score			
Motor coordination	6.7±2.3	8.2±2.5	<0.001
Visual perception	6.5±2.4	7.9±2.1	0.02
Visual-motor integration	7.1±2.4	7.9±1.8	0.02
Audiovisual function (no. of children)			
Visual impairment	12	7	NS
Hearing impairment	18	12	NS

* Plus-minus values are means ±SD. NS denotes nonsignificant. Scores on the Movement Assessment Battery for Children range from 0 to 15 for manual dexterity and for balance, from 0 to 10 for ball skills, and from 0 to 40 overall, with lower scores indicating better performance. Scores for visual-motor performance range from 0 to 9 for each subtest, with higher scores indicating better performance. The performance score for each child was adjusted for age.

sons. The immediate results and the outcomes in early childhood have varied from study to study.¹⁻²¹ It is difficult to interpret these results, because each of these studies was designed differently, not only in terms of the time at which therapy was initiated, but also in terms of the dose and duration of therapy and the sample size. In a systematic review, Barrington¹³ reported an increase in the risk of cerebral palsy and neurodevelopmental impairment associated with glucocorticoid therapy. Halliday and Ehrenkranz^{11,12,16} reviewed the results of randomized, controlled trials from various data bases (studies in early childhood) and concluded that the benefits of postnatal glucocorticoid therapy, either early (initiated within 96 hours after birth) or delayed (initiated after three weeks), may not outweigh the actual or potential adverse effects on neurologic outcome.

Our study was conducted in a double-blind fashion and involved a population that was relatively homogeneous with respect to race and family socio-

economic background. The size of the sample was appropriate, and the proportions of infants in each group who subsequently received open-label glucocorticoid therapy were similar. Even if we had excluded from the analysis the infants who received such therapy, the incidence of disability would still have been significantly higher in the dexamethasone group than in the control group (27 of 66 [41 percent] vs. 14 of 67 [21 percent], $P=0.02$).

Our results show consistent adverse effects of dexamethasone at school age. Among the 42 children (26 in the dexamethasone group and 16 in the control group) who had had neuromotor dysfunction at two years of age, most of those with mild dysfunction showed some improvement at school age (5 of 8, or 62 percent, in the dexamethasone group and 6 of 9, or 67 percent, in the control group). In contrast, none of the children who had had severe neuromotor dysfunction at two years of age showed significant improvement.

Children in the dexamethasone group tended to have more abnormalities of neurologic development and significantly poorer motor performance than children in the control group. This poor motor performance may be responsible for their poor motor coordination and poor visual-motor integration. Our results are consistent with observations by Bos et al.³⁰ in that dexamethasone may impair motility and the quality of general movement in preterm infants. The mechanism behind the neuromotor abnormalities is not completely clear. In experiments in neonatal animals, pharmacologic doses of dexamethasone have resulted in adverse effects on brain-cell division, differentiation, myelination, and electrophysiological reactions.³¹⁻³³

A recent study by Murphy et al.³⁴ suggested that postnatal dexamethasone therapy may cause a decrease in the volume of cerebral gray matter. Such a decrease could explain our finding of subnormal head circumference in the children in the dexamethasone group. Subnormal head size has been shown to be associated with poor cognitive outcome.³⁵ In our study, the children with clinically significant disability had significantly smaller head circumference than those without disability ($49.1±3.0$ vs. $50.8±2.5$, $P<0.001$). The Vermont Oxford Network Steroid Study⁸ and the study by Shinwell et al.¹⁰ have shown a trend toward an increased risk of periventricular leukomalacia associated with dexamethasone therapy.

The WISC-III scores obtained in this study were lower than those that have been reported in other

studies.^{29,35,36} We did not have an established standard for Chinese children; the racial, ethnic, or cultural bias of the tests might explain the low scores in our population. However, the IQ scores in the dexamethasone group were significantly lower than those in the control group. This difference between the groups was not detected in our earlier follow-up study at two years of age, when the children were assessed with use of the Bayley Scales of Infant Development. This discrepancy could be due to a difference in the contents of the tests: the Bayley test focuses much more on motor skills, whereas the IQ test for school-age children focuses much more on cognition. The difference in cognitive function between the two groups could become larger as the children get older. Poor motor function in the dexamethasone-treated children might also affect their cognitive performance.

Neonatal infection and hypertension secondary to dexamethasone therapy could also lead to delayed cognitive function. During the initial study, the incidence of neonatal infection was higher in the dexamethasone group than in the control group. However, among the children included in the current study, the proportions in each group who had had neonatal infections were similar, because many of the infants in the dexamethasone group who had neonatal infections died during the course of the initial study. Neonatal hypertension in the dexamethasone group was usually transient. It is unlikely that neonatal infection or hypertension could account for the higher incidence of cognitive delay in the dexamethasone group in the current study population.

Concern has been expressed regarding the effects of early dexamethasone therapy on somatic growth, because glucocorticoids have been shown to alter cell size and DNA synthesis in animal models.^{32,33} Moreover, Weiler et al.³⁷ and Gibson et al.³⁸ have found that dexamethasone therapy may compromise the accretion of bone mineral and thus affect the velocity of bone growth, even when energy intake increases. Interestingly, the majority of the children who had a delay in growth at school age (26 of 32, or 81 percent) were already short (with a height below the 10th percentile) at two years of age. It appears that the primary or secondary effects of dexamethasone on growth still prevail at school age. Whether dexamethasone can alter the normal acceleration of growth at puberty and ultimately affect the adult stature remains to be clarified.

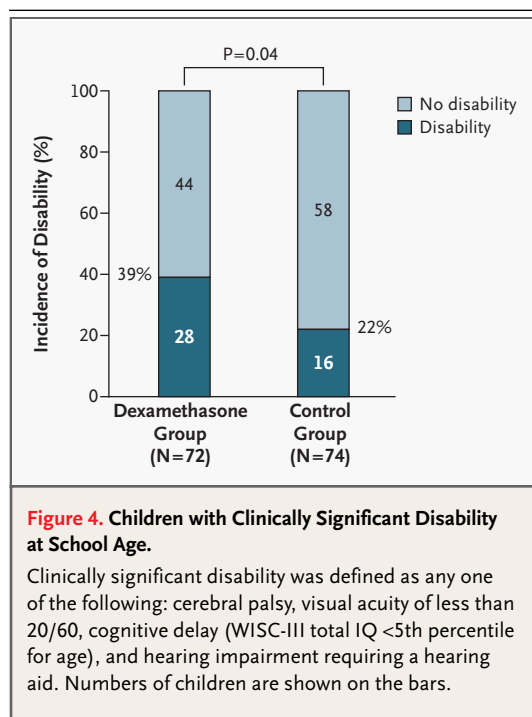
Table 3. Cognition and School Performance.*

Variable	Dexamethasone Group (N=72)	Control Group (N=74)	P Value
Cognition			
WISC-III main scales			
Full IQ	78.2±15.0	84.4±12.6	0.008
Verbal IQ	84.1±13.2	88.4±11.8	0.04
Performance IQ	76.5±14.6	84.5±12.7	0.001
WISC-III subscale score			
Verbal comprehension	84.9±13.1	87.6±12.9	0.21
Perceptual organization	78.0±16.5	85.4±12.4	0.003
Freedom from distractibility	86.8±14.8	96.8±13.4	0.001
Processing speed	83.2±16.8	91.0±15.9	0.005
School performance			
Arithmetic score†	14.7±7.0	17.6±8.2	0.02
Chinese-language aptitude test (T score)‡			
Phonetic transcription and perception	47.9±10.6	52.3±9.5	0.009
Grammar	54.3±8.2	58.3±9.4	0.007
Auditory memory	50.6±12.4	49.2±10.4	NS
Auditory comprehension	51.2±10.7	52.0±9.8	NS
Reading comprehension	54.3±9.1	53.7±9.8	NS
Semantic discrimination	50.8±10.5	48.5±7.5	NS
Wording	53.0±6.2	51.9±7.6	NS
Behavior adaptation score†			
Communication	80.8±19.3	75.9±21.5	NS
Self-care	40.8±18.2	39.7±22.1	NS
Home living	60.1±21.3	72.5±21.9	NS
Social skills	88.9±12.2	85.5±18.6	NS
Use of community resources	65.4±25.3	62.4±23.6	NS
Self-direction	75.3±16.9	71.9±19.2	NS
Health and safety	82.5±15.0	78.7±21.2	NS
Functional academic skills	79.3±19.2	79.9±20.2	NS
Recreational activities	87.9±12.0	87.6±11.3	NS
Schoolwork	68.4±19.3	69.1±20.6	NS

* Plus-minus values are means ±SD. NS denotes nonsignificant. The verbal comprehension subscale of the Wechsler Intelligence Scale for Children, third edition (WISC-III), includes information processing, similarities, vocabulary, and comprehension; the perceptual organization subscale includes picture completion, picture arrangement, block design, and object assembly; the freedom from distractibility subscale includes arithmetic and a digit-span test; and the processing speed subscale includes coding and symbol searching.

† The range in arithmetic scores is from 0 to 36, and in behavior adaptation scores, from 0 to 100.

‡ The original score on the Chinese-language aptitude test was normalized to a T score with a mean of 50 and a standard deviation of 10. A normalized T score indicates the relative position of a person in the population.



The dexamethasone-treated children also had lower scores on arithmetic tests and on tests of phonetic transcription and grammar — findings that are consistent with poorer cognitive function. The testing of Chinese language skills is quite complicated, since spelling ability, pronunciation, and character drawing must be evaluated independently. Moreover, many factors may influence the language and school performance of a child. The most im-

portant factor in our society is probably the pressure and expectations of academic excellence on the part of the family. Many families, particularly those who have disabled children, employ tutors or send their children to special classes to improve their academic performance; therefore, the performance shown in this study might not reflect the children's mental development as accurately as it would have without these aids.

In conclusion, although dexamethasone therapy initiated soon after birth, given at the initial dose for one week and tapered over the next three weeks, significantly reduced the incidence of chronic lung disease in preterm infants with severe respiratory distress syndrome,¹ this therapeutic regimen should not be recommended because of its adverse effects on neuromotor and cognitive function and somatic growth at school age. Our data support the recommendations of the European Association of Perinatal Medicine³⁹ and those of the American Academy of Pediatrics and the Canadian Paediatric Society⁴⁰: routine systemic dexamethasone should not be used postnatally to prevent or treat chronic lung disease of prematurity.

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REFERENCES

1. Yeh TF, Lin YJ, Hsieh WS, et al. Early postnatal dexamethasone therapy for the prevention of chronic lung disease in preterm infants with respiratory distress syndrome: a multicenter clinical trial. *Pediatrics* 1997;100:715-6. abstract. (Also available at <http://www.pediatrics.org/cgi/content/full/100/4/e3>.)
2. Mammel MC, Green TP, Johnson DE, Thompson TR. Controlled trial of dexamethasone therapy in infants with bronchopulmonary dysplasia. *Lancet* 1983;1:1356-8.
3. Avery GB, Fletcher AB, Kaplan M, Brudno DS. Controlled trial of dexamethasone in respirator-dependent infants with bronchopulmonary dysplasia. *Pediatrics* 1985;75:106-11.
4. Dexamethasone therapy in neonatal chronic lung disease: an international placebo-controlled trial. *Pediatrics* 1991;88:421-7.
5. Garland JS, Alex CP, Pauly TH, et al. A three-day course of dexamethasone therapy to prevent chronic lung disease in ventilated neonates: a randomized trial. *Pediatrics* 1999;104:91-9.
6. Rastogi A, Akintorin SM, Bez ML, Morales P, Pildes RS. A controlled trial of dexamethasone to prevent bronchopulmonary dysplasia in surfactant-treated infants. *Pediatrics* 1996;98:204-10.
7. Cummings JJ, D'Eugenio DB, Gross SJ. A controlled trial of dexamethasone in preterm infants at high risk for bronchopulmonary dysplasia. *N Engl J Med* 1989;320:1505-10.
8. Vermont Oxford Network Steroid Study Group. Early postnatal dexamethasone therapy for the prevention of chronic lung disease. *Pediatrics* 2001;108:741-8.
9. Yeh TF, Lin YJ, Huang CC, et al. Early dexamethasone therapy in preterm infants: a follow-up study. *Pediatrics* 1998;101:917. abstract. (Also available at <http://www.pediatrics.org/cgi/content/full/101/5/e7>.)
10. Shinwell ES, Karplus M, Reich D, et al. Early postnatal dexamethasone treatment and increased incidence of cerebral palsy. *Arch Dis Child Fetal Neonatal Ed* 2000;83:F177-F181.
11. Halliday HL, Ehrenkranz RA. Early postnatal (<96 hours) corticosteroids for preventing chronic lung disease in preterm infants. *Cochrane Database Syst Rev* 2000;2:CD001146.
12. *Idem*. Delayed (>3 weeks) postnatal corticosteroids for chronic lung disease in preterm infants. *Cochrane Database Syst Rev* 2000;2:CD001145.
13. Barrington KJ. The adverse neuro-developmental effects of postnatal steroids in the preterm infant: a systematic review of RCTs. *BMC Pediatr* 2001;1:1.
14. O'Shea TM, Kothadia JM, Klinepeter KL, et al. Randomized placebo-controlled trial of a 42-day tapering course of dexamethasone to reduce the duration of ventilator

- dependency in very low birth weight infants: outcome of study participants at 1-year adjusted age. *Pediatrics* 1999;104:15-21.
15. Stark AR, Carlo WA, Tyson JE, et al. Adverse effects of early dexamethasone treatment in extremely-low-birth-weight infants. *N Engl J Med* 2001;344:95-101.
16. Halliday HL, Ehrenkranz RA. Moderately early (7-14 days) postnatal corticosteroids for preventing chronic lung disease in preterm infants. *Cochrane Database Syst Rev* 2001;1:CD001144.
17. O'Shea TM, Kothadia JM, Klinepeter KL, Goldstein DJ, Jackson B, Dillard RG. Follow-up of preterm infants treated with dexamethasone for chronic lung disease. *Am J Dis Child* 1993;147:658-61.
18. Jones R, Wincott E, Elbourne D, Grant A. Controlled trial of dexamethasone in neonatal chronic lung disease: a 3-year follow-up. *Pediatrics* 1995;96:897-906.
19. Romagnoli C, Zecca E, Luciano R, Torrioli G, Tortorolo G. A three year follow up of preterm infants after moderately early treatment with dexamethasone. *Arch Dis Child Fetal Neonatal Ed* 2002;87:F55-F58.
20. *Idem*. Controlled trial of early dexamethasone treatment for the prevention of chronic lung disease in preterm infants: a 3-year follow-up. *Pediatrics* 2002;109:1161. abstract. (Also available at <http://www.pediatrics.org/cgi/content/full/109/6/e85>.)
21. Armstrong DL, Penrice J, Bloomfield FH, Knight DB, Dezoete JA, Harding JE. Follow up of a randomised trial of two different courses of dexamethasone for preterm babies at risk of chronic lung disease. *Arch Dis Child Fetal Neonatal Ed* 2002;86:F102-F107.
22. Henderson SE, Sugden DA. Movement assessment battery for children. London: Psychological Corporation, 1992.
23. Beery KE. The Beery-Buktenica developmental test of visual-motor integration (VMI) with supplemental developmental test of visual perception and motor coordination: administration, scoring and teaching manual. 4th ed. rev. Cleveland: Modern Curriculum Press, 1997.
24. Mayer RE. Thinking, problem solving, cognition. 2nd ed. New York: W.H. Freeman, 1992.
25. Wu WD, Chang CF. The construction of the Chinese language test. *Psychol Testing (TAIWAN)* 2001;31:37-52. (In Chinese.)
26. Shyu S. The construction of the Chinese adaptive behavior scale. *Psychol Testing (TAIWAN)* 1998;45:137-59. (In Chinese.)
27. Kaufman AS, Kaufman NL. Kaufman assessment battery for children: interpretive manual. Circle Pines, Minn.: American Guidance Service, 1983.
28. Luckasson R, Coulter D, Polloway EA, et al. Mental retardation: definition, classification and systems of support. 9th ed. Washington, D.C.: American Association on Mental Retardation, 1992.
29. Robertson CM, Etches PC, Goldson E, Kyle JM. Eight-year school performance, neurodevelopmental, and growth outcomes of neonates with bronchopulmonary dysplasia: a comparative study. *Pediatrics* 1992;89:365-72.
30. Bos AF, Dibiasi J, Tiessen AH, Bergman KA. Treating preterm infants at risk for chronic lung disease with dexamethasone leads to an impaired quality of general movements. *Biol Neonate* 2002;82:155-8.
31. Weichsel ME Jr. The therapeutic use of glucocorticoid hormones in the perinatal period: potential neurological hazards. *Ann Neurol* 1977;2:364-6.
32. Cotterrell M, Balazs R, Johnson AL. Effects of corticosteroids on the biochemical maturation of rat brain: postnatal cell formation. *J Neurochem* 1972;19:2151-67.
33. Weichsel ME. Glucocorticoid effect upon thymidine kinase in the developing cerebellum. *Pediatr Res* 1974;8:843-7.
34. Murphy BP, Inder TE, Huppi PS, et al. Impaired cerebral cortical gray matter growth after treatment with dexamethasone for neonatal chronic lung disease. *Pediatrics* 2001;107:217-21.
35. Hack M, Breslau N, Weissman B, Aram D, Klein N, Borawski E. Effect of very low birth weight and subnormal head size on cognitive abilities at school age. *N Engl J Med* 1991;325:231-7.
36. Saigal S, Szatmari P, Rosenbaum P, Campbell D, King S. Cognitive abilities and school performance of extremely low birth weight children and matched term control children at age 8 years: a regional study. *J Pediatr* 1991;118:751-60.
37. Weiler HA, Paes B, Shah JK, Atkinson SA. Longitudinal assessment of growth and bone mineral accretion in prematurely born infants treated for chronic lung disease with dexamethasone. *Early Hum Dev* 1997;47:271-86.
38. Gibson AT, Pearse RG, Wales JK. Growth retardation after dexamethasone administration: assessment by knemometry. *Arch Dis Child* 1993;69:505-9.
39. Halliday HL. Guidelines on neonatal steroids. *Prenat Neonat Med* 2001;6:371-3.
40. Committee on Fetus and Newborn. Postnatal corticosteroids to treat or prevent chronic lung disease in preterm infants. *Pediatrics* 2002;109:330-8.

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