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Postnatal Corticosteroids to Treat or Prevent Chronic Lung Disease in Preterm Infants

ABSTRACT. This statement is intended for health care professionals caring for neonates and young infants. The objectives of this statement are to review the short- and long-term effects of systemic and inhaled postnatal corticosteroids for the prevention or treatment of evolving or established chronic lung disease and to make recommendations for the use of corticosteroids in infants with very low birth weight. The routine use of systemic dexamethasone for the prevention or treatment of chronic lung disease in infants with very low birth weight is not recommended.

ABBREVIATIONS. CLD, chronic lung disease; VLBW, very low birth weight; PMA, postmenstrual age; PNA, postnatal age; NEC, necrotizing enterocolitis; PVL, periventricular leukomalacia, CI, confidence interval.

BACKGROUND

Chronic lung disease (CLD), also known as bronchopulmonary dysplasia, is an important cause of mortality and morbidity in preterm infants.^{1,2} The incidence of CLD among surviving infants with very low birth weight ([VLBW]; birth weight <1500 g) in 2 large databases was 26% in Canada (1996–1997)¹ and 23% in the United States (1995–1996).² CLD is usually defined as oxygen dependency at 36 weeks' postmenstrual age (PMA) or 28 days' postnatal age (PNA), in conjunction with persistent clinical respiratory symptoms and compatible abnormalities on chest radiographs.^{3–6}

Because inflammation plays an important role in the pathogenesis of CLD, corticosteroids, in particular dexamethasone, have been widely used to prevent or treat CLD.^{1,2,7} Postnatal corticosteroids were given to 25% of infants with VLBW in Canada (1996–1997)¹ and 19% in the United States (1995–1996).² Corticosteroid use is higher in infants with birth weight <1000 g.^{1,2} Numerous studies suggest that systemic corticosteroids decrease the duration of ventilator dependence.^{8–16} However, early beneficial effects on the pulmonary system may be outweighed by an increased risk of serious short- and long-term adverse effects.^{8–24}

The recommendations in this statement do not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

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OBJECTIVES

The objectives of this statement are to review the short- and long-term effects of systemic and inhaled postnatal corticosteroids for the prevention or treatment of evolving or established CLD and to make recommendations for the use of corticosteroids in infants with VLBW. The focus of this statement will be limited to the use of corticosteroids in neonates with VLBW for the prevention or treatment of CLD.

LITERATURE REVIEW

An attempt was made to identify all published systematic reviews and meta-analyses on the use of corticosteroids (systemic or inhaled) for the prevention or treatment of CLD in preterm infants, using the MEDLINE, EMBASE, CINAHL, and Cochrane Library electronic databases and personal files from 1983 through April 2001. Data were also included from 2 trials published after the identified systematic reviews.^{19,25} Twelve systematic reviews published between 1992 and 2001 were identified.^{8–16,26–28} Nine addressed the use of systemic steroids,^{8–11,13–16,28} 2 described the use of inhaled steroids,^{26,27} and 1 addressed both.¹² Numerous outcomes were evaluated. The results are presented in 5 sections: the first 3 sections report on the effects of systemic corticosteroids on the basis of age at which the infants were treated, the fourth section reports on the effects of inhaled steroids, and the fifth section describes the effects of systemic corticosteroids on neurodevelopmental outcomes.

Systemic Early Postnatal Corticosteroid Therapy (<96 Hours of Age)

The most complete systematic reviews were published in 2001.^{13,16} In addition, the meta-analysis for systemic early postnatal corticosteroid therapy by Shah and Ohlsson¹⁶ was updated by incorporating data from 2 subsequently published studies.^{19,25} Infants studied were preterm, demonstrated respiratory distress syndrome on chest radiographs, and required mechanical ventilation with oxygen at the time of enrollment.^{8–11,13,16,19,25} Systemic corticosteroids were given intravenously within 96 hours after birth; dexamethasone was used in all but 2 studies.^{29,30} The most commonly used dosages were 0.5 mg/kg of body weight per day for 3 days, followed by a tapering course of 0.25, 0.125, and 0.05 mg/kg

per day each for 3 days.^{13,16} One study¹⁹ used a considerably lower dosage (0.15 mg/kg per day for 3 days, 0.10 mg/kg per day for 3 days, 0.05 mg/kg per day for 2 days, and 0.02 mg/kg per day for 2 days). The combined outcome of death or CLD at 28 days' PNA or at 36 weeks' PMA^{13,16} was significantly decreased by early corticosteroid treatment. There was no effect on mortality at 28 days' PNA, at 36 weeks' PMA, or at discharge.^{13,16} Corticosteroid treatment decreased CLD incidence at 28 days' PNA and at 36 weeks' PMA.^{8–11,13,16} On the basis of an analysis including data from the most recently published trials,^{19,25} 10 infants would need to be treated with corticosteroids to prevent 1 from developing CLD at 28 days' PNA or at 36 weeks' PMA.

Weaning from mechanical ventilation was more successful in infants treated with dexamethasone.^{13,16} The use of additional systemic dexamethasone by clinicians outside of the study protocols (open-label use) was decreased.^{13,16}

The incidences of hypertension,¹⁶ hyperglycemia,¹³ insulin therapy for hyperglycemia,¹⁶ gastrointestinal bleeding¹⁶ or perforation,¹³ and hypertrophic obstructive cardiomyopathy¹³ were increased by early corticosteroid treatment. The rates of pulmonary air leaks¹³ and patent ductus arteriosus were decreased.^{13,16} There was no difference in the incidence of infection,^{13,16} necrotizing enterocolitis (NEC),¹⁶ intraventricular hemorrhage,^{13,16} or severe retinopathy of prematurity.^{13,16} Weight gain was decreased during dexamethasone therapy.^{13,16} A borderline increased risk of periventricular leukomalacia (PVL) in the infants who received dexamethasone was noted in 1¹³ but not in the other recent systematic review.¹⁶ In an update of the review by Shah and Ohlsson,¹⁶ including the 2 recently published studies ($n = 1096$),^{19,25} the relative risk of PVL was 1.41 (95% confidence interval [CI]: 0.93–2.13). Long-term outcomes are shown in Table 1.

Systemic Moderately Early Postnatal Corticosteroid Therapy (7–14 Days' PNA)

The most current reviews were published in 2001.^{14,16} Infants in the studies included in the meta-analyses were preterm and dependent on mechanical ventilation with oxygen at enrollment.^{9–11,14,16} All trials used dexamethasone. The drug was administered intravenously for 2 to 42 days, starting at between 7 and 14 days of age or given as a pulse dose for 3 days at 10-day intervals until the infant no longer required supplemental oxygen or ventilation or had reached 36 weeks' PMA. The initial dosage was 0.5 mg/kg per day, which was maintained for the duration of the study period, decreased over 7 to 42 days, or followed by inhaled budesonide.^{9,14,16}

The combined outcome of death or CLD was decreased at 28 days' PNA and at 36 weeks' PMA.^{14,16} Mortality was not decreased in the treatment group at the time of discharge.^{14,16} In 1 review, mortality was not decreased at 28 days' PNA or 36 weeks' PMA¹⁶; the other showed decreased mortality at 28 days' PNA.¹⁴ The incidence of CLD at 28 days' PNA and 36 weeks' PMA^{14,16} was decreased. The number

of infants that needed to be treated with dexamethasone was 7 and 4 to prevent CLD at 28 days' PNA and 36 weeks' PMA, respectively.¹⁶ Infants were more likely to be extubated by 7 and 28 days after initiation of treatment with dexamethasone.^{14,16} However, the duration of hospitalization or need for supplemental oxygen was not decreased.¹⁶ The subsequent use of additional systemic steroids in the infants who had received dexamethasone during the study period was decreased.^{14,16}

The incidences of pneumothorax, severe retinopathy of prematurity, intraventricular hemorrhage, and NEC were not increased.^{14,16} Infants in the dexamethasone group had an increased risk of developing hypertension.^{14,16} The 2 reviews differed in reporting statistically significant differences between treatment and control groups for hyperglycemia, gastrointestinal bleeding, hypertrophic obstructive cardiomyopathy, and infection.^{14,16} Long-term outcomes are shown in Table 2.

Systemic Delayed Postnatal Corticosteroid Therapy (>3 Weeks)

There are 2 overlapping systematic reviews on systemic corticosteroid use started after 3 weeks of age.^{12,15} All infants enrolled in the primary studies were preterm and were dependent on oxygen or mechanical ventilation at approximately 3 weeks or beyond, with or without abnormalities of CLD evident on chest radiographs. Dexamethasone was administered intravenously or enterally at 0.5 to 1 mg/kg per day for a duration of 3 days to 3 weeks. The dosage was then tapered every 3 days in different ways; in some studies, the infants subsequently received hydrocortisone.

The combined outcome of death or CLD at 36 weeks' PMA was decreased by dexamethasone treatment. Dexamethasone did not affect survival at discharge or duration of hospitalization, but fewer infants were discharged from the hospital on oxygen therapy. Extubation was facilitated by 7 and 28 days after initiation of the treatment. Dexamethasone also improved respiratory compliance and decreased the need for oxygen supplementation, resulting in a borderline significant decrease in the incidence of CLD at 36 weeks' PMA. Late rescue treatment with dexamethasone was decreased in the treated infants. The risk of hypertension was increased by dexamethasone, but there was no difference in incidence of infection, NEC, or gastrointestinal bleeding, compared with controls. More infants in the dexamethasone group than in the control group experienced poor weight gain or even weight loss.^{12,15} Long-term outcomes are shown in Table 3.

Inhaled Steroids

Two systematic reviews address the effectiveness of inhaled corticosteroids to prevent CLD in ventilated infants with VLBW enrolled within 2 weeks after birth.^{12,26} No benefit of inhaled corticosteroids was shown, except the borderline significant decrease of subsequent administration of systemic dexamethasone. It is uncertain whether inhaled corticosteroids simply do not work for this condition or

TABLE 1. Neurodevelopmental Outcome Data for Early (<96 Hours) Postnatal Corticosteroid Use for Prevention of CLD

Author	Drug, Dosage, and Duration of Therapy	Number of Patients Enrolled	Outcome Data
Fitzhardinge et al, 1974 ³⁹ ; original study by Baden et al, 1972 ²⁹	Hydrocortisone (12.5 mg/kg of body weight) was administered 12 h apart in the first 24 h, or 2 placebo injections of a lactose solution were administered.	44	28 of 44 survived the neonatal period. 24 of 28 were evaluated for a minimum of 1 year. Follow-up data were not available on 2 subjects. 1 control infant died at 10 months with microcephaly and extensive brain damage. 1 study infant limited data obtained by letter. 3 of 13 infants in the steroid group had evidence of neuromotor dysfunction (1 had moderate degree of spastic quadriplegia, 1 had hypotonia and slow motor development, and 1 had increased extensor tone and slow motor development). 2 of 13 infants in the placebo group had evidence of neuromotor dysfunction (1 had mild spastic diplegia, 1 had microcephaly, and spastic diplegia [RR: 1.50; 95% CI: 0.30–7.55]). 4 of 13 infants in the steroid group had EEG abnormalities (mild paroxysmal changes with no epileptiform patterns). No EEG abnormalities were noted in the placebo group. Mean developmental quotient (using Griffith Developmental Scale): no statistically significant differences were noted between groups (steroid group, 95.4 vs placebo group, 97.9). Locomotor scale: there was a significant difference in the results for gross motor development (steroid group, 93 vs placebo group, 104 [$P < .05$]).
Stark et al, 2001 ⁴¹ ; original study by Stark et al, 2001 ¹⁹	Dexamethasone was administered within 24 h after birth (0.15 mg/kg per day for 3 d, then tapered over 7 d), or placebo was administered.	220	Of the 166 survivors, 123 (74%) were evaluated at 18 to 22 mo of age using the BSID II, a standardized neurologic exam and hearing and vision assessment. Neurodevelopmental impairment was defined as a Bayley score <70, abnormal neurologic examination, or deafness or blindness. 34 of 67 in the steroid group had MDI of <70, compared with 24 of 56 in the placebo group (RR: 1.18; 95% CI: 0.81–1.74). 20 of 67 in the steroid group had PDI of <70, compared with 20 of 56 in the placebo group (RR: 0.84; 95% CI: 0.50–1.39). Abnormal neurologic exam was noted in 17 of 67 infants in the steroid group, compared with 14 of 56 infants in the placebo group (RR: 1.02; 95% CI: 0.55–1.87). Of the 195 infants who survived to discharge, 5 died in the postneonatal period. Follow-up data were obtained on 159 of 190 (84%) survivors at a mean (\pm SD) age of 53 \pm 18 mo. 31 were lost to follow-up (10 in the placebo group and 21 in the steroid group). As detailed Bayley, Griffith, or other developmental assessments were not available in all cases, developmental status was defined as normal, mildly abnormal, or severely abnormal. Severe abnormality was defined as any of the following: motor disability in children who were not independently ambulatory, global retardation, deafness requiring hearing aids, and blindness. 39 of 80 infants in the steroid group developed cerebral palsy, compared with 12 of 79 in the placebo group (RR: 3.21; 95% CI: 1.82–5.66).
Shinwell et al, 2000 ³⁸	Dexamethasone was administered (0.5 mg/kg per day) in 2 divided doses for 3 d (administered before 12 h of age), or saline placebo was administered.	248	Spastic diplegia was the most common form of cerebral palsy noted. 44 of 80 infants in the steroid group were noted to have developmental delay, compared with 23 of 79 in the placebo group (RR: 1.89; 95% CI: 1.27–2.81). No differences were found in visual or hearing problems between groups.

TABLE 1. Continued

Author	Drug, Dosage, and Duration of Therapy	Number of Patients Enrolled	Outcome Data
Subheddar et al, 2000 ⁴⁰	Dexamethasone was administered at 96 h of age (1 mg/kg per day for 3 d, then 0.5 mg/kg per day for 3 d). For 3 infants, the starting dosage was decreased to 0.5 mg/kg per day because of an observed increase in gastrointestinal adverse effects. No placebo was administered.	42	Of the 42 infants in the trial, 20 died (17 before discharge and 3 in the postneonatal period). Detailed assessment was performed in 21 of the 22 survivors at 30 mo of age (1 was lost to follow-up) using BSID II. Cerebral palsy was defined as the presence of any abnormal motor signs. Developmental delay was defined as MDI or PDI <70. Severe neurodisability was defined as cerebral palsy with or without significant developmental delay and with or without significant visual or hearing impairment. Cerebral palsy was noted in 0 of 10 infants in the steroid group, compared with 2 of 11 in the control group (RR: 0.22; 95% CI: 0.01–4.06). Significant developmental delay was noted in 0 of 10 in the steroid group, compared with 4 of 11 in the control group (RR: 0.12; 95% CI: 0.01–2.00). Severe neurodisability was noted in 1 of 10 infants in the treated group, compared with 4 of 11 in the control group (RR: 0.28; 95% CI: 0.04–2.07).
Yeh et al, 1998 ³¹	Dexamethasone administration commenced at <12 h of age (0.5 mg/kg per day for 7 d, then 0.24 mg/kg per day for 7 d, then 0.1 mg/kg per day for 7 d, and then 0.04 mg/kg per day for 7 d), or saline placebo was administered.	270	Of the 270 infants included in the initial study, 8 were excluded from data analysis (6 died from culture-proven sepsis within 12 h after birth, 2 had severe asphyxia), and 83 infants died in the neonatal period. Of the 179 survivors, 9 infants in the control group and 13 in the steroid treated group were lost to follow-up. Follow-up data at 2 years of age is available for 133 of 157 patients (in 9 infants, follow-up study could not be completed because of lack of parental consent or cooperation from the child). In addition, 15 infants died in the postneonatal period. Neuromotor dysfunction was classified as mild, moderate, or severe on the basis of mobility of the child. EEG was also performed including visual stimulation and auditory stimulation. Psychometric evaluations were performed using BSID II. 25 of 63 infants in the steroid group had neuromotor dysfunction, compared with 12 of 70 in the control group (RR: 2.32; 95% CI: 1.27–4.21). Significant handicap, defined as severe neurologic defect and/or intellectual defects (MDI and/or PDI <70), was seen in 26 of 63 in the steroid group, compared with 22 of 70 in the control group (RR: 1.31; 95% CI: 0.83–2.07).

RR indicates relative risk*; EEG, electroencephalography; BSID II, Bayley Scales of Infant Development II; MDI, mental developmental index; PDI, psychomotor developmental index.

*RR and 95% CI were calculated using SAS Version 8 for Windows (SAS Institute Inc, Cary, NC). When there was no outcome event in 1 group, 0.5 was added to each cell to calculate the RR.

TABLE 2. Neurodevelopmental Outcome Data for Moderately Early (7–14 Days) Postnatal Corticosteroid Use for Prevention of CLD

Author	Drug, Dosage, and Duration of Therapy	Number of Patients Enrolled	Outcome Data
Cummings et al, 1989 ³²	Dexamethasone was administered to infants at 14 d of age (0.5 mg/kg per day for 3 days, then 0.3 mg/kg per day for 3 d, and then decreased by 10% every 3 d until 0.1 mg/kg per day was administered for 3 d, and then 0.1 mg/kg per day on alternate days for 1 wk [total duration of therapy, 42 d]; or in a dose of 0.5 mg/kg per day for 3 d and then decreased by 50% every 3 d to 0.06 mg/kg per day for 3 d and then 0.06 mg/kg per day on alternate days for 1 week [total duration of therapy, 18 d]), or placebo was administered.	36	Neurodevelopmental outcomes were assessed at 6 and 15 mo of age. Developmental evaluations were made using BSID II. Good neurologic outcome was defined as normal neurologic findings and Bayley mental and psychomotor indices ≥ 84 . 23 of 36 (64%) survived to discharge. Good outcome was noted in 7 of 9 infants in the 42-d course, 2 of 9 infants in the 18-d course, and 2 of 5 in the placebo group ($P < .05$). The results for bad outcome in the 2 groups that were given steroids were combined and compared with the placebo group (RR: 0.83; 95% CI: 0.36–1.95).
Hofkosh et al 1995 ⁴² ; original study by Brozanski et al, 1995 ⁴³	Infants with VLBW who were ventilator-dependent at 7 d PNA were randomly assigned to receive pulse doses of dexamethasone (0.5 mg/kg per day, divided twice daily [$n = 39$] or saline placebo [$n = 39$], for 3 days at 10-d intervals until they no longer required supplemental oxygen or ventilation or reached 36 wk PMA.	78	65 infants survived to term. 44 were available for follow-up at 12 mo adjusted age (25 in the dexamethasone group and 19 in the control group). Outcome measures included MDI and PDI indices of the BSID II. Mean (\pm SD) MDI was 89.5 ± 23.7 in the dexamethasone group and 80.8 ± 26.0 in the control group ($P = .18$). PDI scores were 87.0 ± 26.1 in the dexamethasone group and 75.2 ± 24.8 in the control group ($P = .14$). Measurements of length, weight, and head circumference did not differ between groups.
O'Shea et al, 1999 ³⁷ ; original study by Kothadia et al, 1999 ³⁶	Dexamethasone administration commenced at between 15 and 25 d of age (0.5 mg/kg per day for 3 d, then 0.3 mg/kg per day for 3 d, and then decreased by 10% every 3 d until 0.1 mg/kg per day was administered for 3 d, and then 0.1 mg/kg per day on alternate days for 1 wk [total duration of therapy, 42 d]), or saline placebo was administered.	118	Neurodevelopmental assessment was performed at 1 y adjusted age using the BSID II, Vineland Adaptive Behavioral scales, a physical and neurologic examination by a developmental pediatrician, and auditory testing. Cerebral palsy was diagnosed only if a pediatrician and a physical therapist agreed on the presence of abnormal control of movement and posture with impaired motor function. Of the 118 infants enrolled in the study, 95 survived to discharge. Follow-up data is available from 93 infants, and 2 parents refused evaluation of their infant. Cerebral palsy was diagnosed in 12 of 48 infants in the steroid group, compared with 3 of 45 in the placebo group (RR: 3.75; 95% CI: 1.13–12.43). No differences were noted between groups for MDI or PDI scores.

TABLE 3. Neurodevelopmental Outcome Data for Late (>3 Weeks of Age) Postnatal Corticosteroid Use for Treatment of CLD

Author	Drug, Dosage, and Duration of Therapy	Number of Patients Enrolled	Outcome Data
Vincer et al, 1998 ³⁵	Dexamethasone was administered after 28 d of age in infants who were ventilator dependent (0.5 mg/kg per day for 3 d and 0.3 mg/kg per day for the final 3 d), or saline placebo was administered.	20	Of the 20 infants enrolled in the study, 11 received dexamethasone and 9 received placebo. 3 infants died before discharge from the hospital (2 from the steroid group and 1 from the placebo group). Cerebral palsy was reported in 4 of 9 in the steroid group versus 2 of 8 in the placebo group (RR: 1.78; 95% CI: 0.44–7.25).
Ohlsson, 1992 ²⁰ ; original study by Ohlsson, 1990 ⁴⁴	Dexamethasone was administered to infants at between 21 and 35 d of age (1 mg/kg per day for 3 d, then 0.5 mg/kg per day for the next 3 d, then 0.25 mg/kg per day for the next 3 d, and then 0.125 mg/kg per day for the last 3 d), or sham injections were given.	25	Outcome data available on 24 of 25 infants enrolled in the study (1 infant died at 238 d). Mean corrected age (\pm SD) was 26.5 \pm 7.8 months in the steroid group versus 28.8 \pm 7.5 mo in the control group. Cerebral palsy was noted in 1 of 11 infants in the steroid group, compared with 3 of 13 in the control group (RR: 0.39; 95% CI: 0.05–3.27). Delayed motor development was noted in 3 of 11 in the treatment group versus 2 of 13 in the control group (RR: 1.77; 95% CI: 0.36–8.77). Bayley scores were 90 \pm 15 in the treatment group, compared with 100 \pm 20 in the control group ($P = .287$).
Jones et al, 1995 ³⁴ ; original study by Collaborative Dexamethasone Trial Group, 1991 ³³	Dexamethasone was administered at between 2 and 12 wk of age (0.5 mg/kg per day for a week), or normal saline placebo was administered. There was an option to administer a second tapering 9-d course of steroids if relapse occurred after the initial improvement.	287	Information regarding cerebral palsy, global retardation, and visual or hearing loss was obtained from healthy visitors and general practitioners. Information from parents was obtained using a questionnaire regarding the use of health services such as physiotherapy, speech therapy, and occupational therapy. Also, information on development from parents was obtained using a Minnesota Child Development Inventory. Follow-up data were obtained on 209 of the 223 survivors at 3 y of age. Cerebral palsy was noted in 20 of 100 infants in the steroid group, compared with 18 of 109 in the placebo group (RR: 1.21; 95% CI: 0.68–2.16). Global retardation was noted in 15 of 100 in the steroid group, compared with 13 of 109 in the placebo group (RR: 1.26; 95% CI: 0.63–2.51).

whether the type, dosage, or delivery methods were inadequate. Other meta-analyses studied infants with VLBW enrolled after 2 weeks of age, with administration of inhaled corticosteroids for 1 to 4 weeks.^{12,27} Inhaled corticosteroids appeared to improve the extubation rate; however, there was heterogeneity between studies for this finding. No other differences were found, possibly because of lack of statistical power. Additional studies may help determine if inhaled corticosteroids decrease the need for systemic treatment or facilitate extubation.

Neurodevelopmental Outcome

Two systematic reviews are available that focus on mortality and long-term neurodevelopment of infants enrolled in randomized, controlled trials of corticosteroids.^{11,28} In 1 review of 5 trials,^{31–37} 475 (91%) of 522 survivors were followed. Mortality was not significantly different in the steroid and control groups.¹¹ Motor dysfunction was significantly greater with postnatal corticosteroid treatment, with an event rate difference of 11.9% favoring the controls (95% CI: 4.6%–19.2%). The rate of survival free of motor dysfunction was lower in the postnatal corticosteroids group (event rate difference, 7.8% favoring controls [95% CI: 0.5%–15.1%]).

Barrington²⁸ identified 3 additional trials^{29,38–40} that reported on long-term outcome after postnatal exposure to corticosteroids. These 8 studies represent 1052 infants; 292 of them died and 679 (89%) of the 760 survivors were followed for 1 year or longer. One important difficulty in evaluating long-term effects of corticosteroids is that many controls were treated with open-label dexamethasone after the initial study period. Barrington²⁸ tried to take this into account by arbitrarily dividing the studies into 2 groups on the basis of whether they had <30% contamination (corticosteroids given to infants in the control group [group 1]), or >30% contamination or did not report on contamination (group 2). The outcomes evaluated were the incidences of cerebral palsy and neurodevelopmental impairment; the latter was defined as a developmental score more than 2 standard deviations below the mean or cerebral palsy or blindness.

The studies demonstrated a relative risk of neurodevelopmental impairment among surviving children exposed to corticosteroids of 1.34 (95% CI: 1.09–1.64), compared with controls.²⁸ In the 4 studies with <30% contamination, the relative risk was 1.66 (95% CI: 1.26–2.19).²⁸ Including all studies, the relative risk of developing cerebral palsy in the surviving infants exposed to corticosteroids was 2.02 (95% CI: 1.51–2.71).²⁸ For infants from studies with <30% contamination, the relative risk of developing cerebral palsy among exposed infants was 2.89 (95% CI: 1.96–4.27).²⁸ Thus, there appears to be a trend in the size of the apparent effect, which decreases as the degree of contamination increases.²⁸

We identified 3 additional trials^{19,20,41–44} that reported long-term outcomes after exposure to corticosteroids for the prevention or treatment of CLD increasing the sample size to a total of 870 children

evaluated at 1 year of age or later (Tables 1–3). The identified trials are heterogeneous in the study populations, timing and dosage of postnatal corticosteroid treatment, crossover rates, event rates in the control groups, follow-up rates, time of assessment of neurodevelopment, and instruments used to assess neurodevelopment. Furthermore, not all are peer-reviewed publications. Discrepancies between results reported in abstracts and full publications of the same randomized, controlled trial are common.⁴⁵ Therefore, the data were not combined using meta-analytic techniques; instead, available details are presented in Tables 1 to 3.

DISCUSSION

Systemic dexamethasone administration with the intent to prevent or treat CLD in the preterm infant does not affect mortality by the time of discharge or length of hospitalization. Early and moderately early systemic administration of dexamethasone decreases the incidence of CLD at 28 days' PNA and 36 weeks' PMA and allows for earlier extubation and fewer ventilator days. However, for these short-term benefits, there are many short-term adverse effects, including hyperglycemia often requiring insulin therapy, hypertension, gastrointestinal bleeding and intestinal perforation, hypertrophic obstructive cardiomyopathy, poor weight gain and poor growth of the head circumference, and a trend toward higher incidence of PVL.

The short-term pulmonary benefits of systemic dexamethasone do not appear to confer long-term benefits. Survival does not improve after dexamethasone administration. Furthermore, data indicating an increased incidence of neurodevelopmental delay and cerebral palsy raise serious concerns about adverse long-term outcomes.

Dexamethasone is a potent anti-inflammatory corticosteroid. The pharmacologic doses commonly used in trials and in practice are more than 10 to 15 times the estimated physiologic secretion rate of cortisol in neonates. Furthermore, the limited pharmacokinetic data available in infants with extremely low birth weight indicate a prolonged half-life of dexamethasone compared with that in children and adults.^{46,47} High levels of dexamethasone may increase the rate of adverse effects. Possible alternatives to dexamethasone that may have fewer adverse consequences include methylprednisolone, low hydrocortisone doses administered before chronic lung changes have developed, or inhaled corticosteroids.⁴⁸ These require additional investigation. However, it is uncertain whether neurodevelopmental abnormalities are linked to the systemic use of corticosteroids in general or just to dexamethasone.²⁸

The additional 3 trials noted in the tables^{19,20,41–44} increased the sample size by 191 children followed compared with the review by Barrington²⁸ and by 395 compared with the review by Doyle and Davis¹¹; this increased sample size would affect the results of the 2 previously published meta-analyses.^{11,28} The results of the 3 additional trials support the concept that corticosteroids should not be used routinely to

prevent or treat infants at high risk of developing CLD or those with established CLD.

In view of the concerns regarding short- and long-term adverse effects, dexamethasone should not be routinely used to prevent or treat CLD. Enough uncertainty remains with regard to short- and long-term benefits and harms of corticosteroids to justify additional well-designed and executed trials that would use a combination of survival and long-term developmental impairments as the primary outcome.

SUMMARY

- Systemic administration of dexamethasone to preterm infants who are mechanically ventilated decreases the incidences of CLD and extubation failure but does not decrease overall mortality.
- Treatment of infants with VLBW with dexamethasone is associated with an increased risk of short- and long-term complications, including impaired growth and neurodevelopmental delay.
- No substantial short- or long-term benefits have been demonstrated from the use of inhaled corticosteroids in the prevention or treatment of CLD.

RECOMMENDATIONS

1. On the basis of limited short-term benefits, the absence of long-term benefits, and the number of serious short- and long-term complications, the routine use of systemic dexamethasone for the prevention or treatment of CLD in infants with VLBW is not recommended.
2. Postnatal use of systemic dexamethasone for the prevention or treatment of CLD should be limited to carefully designed randomized double-masked controlled trials. The primary outcome of these trials should be survival without long-term developmental impairments, and the potential confounders of contamination and crossover should be avoided.
3. Long-term neurodevelopmental assessment of infants who are or have been subjects in trials of dexamethasone to prevent or treat CLD is strongly encouraged.
4. Clinical trials investigating the use of alternative anti-inflammatory corticosteroids, systemic and inhaled, are required before additional recommendations can be made.
5. Outside the context of a randomized, controlled trial, the use of corticosteroids should be limited to exceptional clinical circumstances (eg, an infant on maximal ventilatory and oxygen support). In those circumstances, parents should be fully informed about the known short- and long-term risks and agree to treatment.

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