treat or prevent chronic lung disease in preterm infants

Ann L Jefferies; Canadian Paediatric Society, Fetus and Newborn Committee
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Abstract
Postnatal corticosteroids have been used for prevention and treatment of neonatal chronic lung disease (CLD) (also known as bronchopulmonary dysplasia), a significant cause of mortality and morbidity in preterm infants. As both dexamethasone and hydrocortisone administration within the first seven days of life is associated with an increased risk of cerebral palsy, early postnatal corticosteroid therapy is not recommended to prevent CLD. After seven days of life, dexamethasone has been shown to decrease the rate of CLD at 36 weeks’ postmenstrual age with less impact on neurodevelopmental outcome. No trials have examined whether the benefits of corticosteroids outweigh the adverse effects for infants at high risk of, or with, severe CLD. While routine dexamethasone therapy of all ventilated infants is not recommended, clinicians may consider a short course of low-dose dexamethasone for individual infants at high risk of or with severe CLD. There is no evidence that hydrocortisone is an effective or safe alternative to dexamethasone and little evidence to support routine use of inhaled corticosteroids for prevention or treatment. Inhaled corticosteroids may be considered as an alternative to dexamethasone for treating individual infants with severe CLD. This revision replaces a statement published jointly with the American Academy of Pediatrics in 2002.

Key Words: Bronchopulmonary dysplasia; Chronic lung disease; Dexamethasone; Postnatal corticosteroids; Preterm infants

Chronic lung disease (CLD), also known as bronchopulmonary dysplasia (BPD), is a significant cause of mortality and morbidity in preterm infants. There are a number of definitions of CLD; one often used is the need for oxygen at 36 weeks’ postmenstrual age (PMA), together with respiratory symptoms and compatible changes on chest radiograph. In 2000, the National Institute of Child Health and Human Development/National Heart, Lung, and Blood Institute provided a new definition which categorized the severity of CLD/BPD, and the predictive validity of this definition has been demonstrated. In Canada, 21% of surviving infants born at less than 33 week’ gestational age (GA) and admitted to 27 special care nurseries required oxygen at 36 weeks’ PMA. Because inflammation plays an important role in the pathogenesis of CLD, corticosteroids, in particular dexamethasone, have been used to prevent or treat CLD.

In 2002, the Canadian Paediatric Society published a statement jointly with the American Academy of Pediatrics, making recommendations about the use of postnatal corticosteroids for prevention or treatment of CLD in low birthweight infants. Prompted by reports of short- and long-term adverse effects of corticosteroids, including poor neurodevelopmental outcome, routine use of systemic dexamethasone for preventing or treating CLD in very low birthweight infants was not recommended. It was recommended that the use of postnatal corticosteroids outside of randomized trials be limited to exceptional circumstances and only with the understanding and agreement of parents.

Since publication of this statement in 2002, use of postnatal corticosteroids has decreased, as reported by three large network registries—the Canadian Neonatal Network, National Institute of Child Health and Development Neonatal Research Network and Vermont Oxford Network. This decrease was not associated with
an increase in mortality or with major short-term morbidities including the need for oxygen at 36 weeks’ PMA. However, more recently, increases in rates of CLD have been reported in Canada and elsewhere.[17][18] CLD has been shown to be an independent risk factor for poor neurodevelopmental outcome.[9] Some clinicians have therefore wondered whether overly restricting the use of corticosteroids may increase morbidity for some preterm infants. Specifically, questions about treatment with lower cumulative doses of dexamethasone, shortened duration of dexamethasone therapy, alternatives to systemic dexamethasone and the treatment only of infants at high risk of CLD have been raised.

Since 2002, new information about the use of dexamethasone and other corticosteroids for preventing or treating CLD has been published. This statement reviews this new information and provides new recommendations for the use of postnatal corticosteroids to prevent and treat CLD. Levels of evidence and grading of recommendations are based on criteria from the Canadian Task Force on Preventive Health Care.[10]

Updated literature
Since 2002, further studies reporting long-term follow-up of infants enrolled in randomized trials have been published and summarized in systematic reviews. Shinwell and Eventov-Friedman analyzed 18 trials that compared dexamethasone with placebo and reported long-term follow-up.[11] The trials were heterogeneous with respect to the start or duration of dexamethasone exposure. Dexamethasone treatment was associated with an increased risk of cerebral palsy (OR 1.63, 95% CI 1.20 to 2.22) and neurodevelopmental impairment (OR 1.40, 95% CI 1.03 to 1.90). Use of early postnatal corticosteroids within the first seven days of life was examined in a 2010 Cochrane review that included studies using dexamethasone (n=20) or hydrocortisone (n=8).[12] and in a systematic review of early dexamethasone therapy written by the same authors.[13] Although early corticosteroids facilitated earlier extubation and reduced the need for oxygen at 36 weeks’ PMA, there were significant short-term adverse effects, including hyperglycemia, hypertension, gastrointestinal hemorrhage and gastrointestinal perforation. The rates of cerebral palsy and the combined outcome of death or cerebral palsy were increased (RR 1.17, 95% CI 1.00 to 1.37) in dexamethasone-treated infants. The impact of dexamethasone in both decreasing rates of CLD and increasing adverse neurodevelopmental outcome was much greater than that of hydrocortisone. In summary, the benefits of early corticosteroid therapy, in particular dexamethasone, did not appear to outweigh the adverse effects (Level 1 evidence).

The effects of late dexamethasone, started after day seven, were analyzed in a 2009 Cochrane review and in a systematic review that included 19 trials.[14][15] Late dexamethasone treatment decreased mortality at 28 days, the rate of CLD at 36 weeks’ PMA, and the combined outcome of death or CLD at 36 weeks (RR 0.72, 95% CI 0.51 to 0.94), as well as decreasing failure to extubate within seven days and the number of infants discharged home on oxygen. Some short-term adverse effects, including hyperglycemia and hypertension, were reported in treated babies, as well as a higher incidence of hypertrophic cardiomyopathy and severe retinopathy of prematurity in the group of infants treated with dexamethasone. The incidence of blindness was not increased. Follow-up data were available from 11 studies comprising 777 infants, and showed no differences in major neurosensory disability, cerebral palsy or combined rates of death or cerebral palsy (RR 0.98, 95% CI 0.80 to 1.21). An increased rate of abnormal neurological examination was reported in four studies (200 infants) but the significance of this finding was unclear. The authors commented that the quality of some of the long-term studies was limited, with many not powered to detect increased rates of adverse neurodevelopmental outcomes. Furthermore, many studies were contaminated by use of open-label steroids in the control group. Because late dexamethasone appeared to have both beneficial and harmful effects, it was suggested that its use be reserved for infants who could not be weaned from mechanical ventilation (Level 1 evidence).

Low-dose dexamethasone
Most studies of dexamethasone therapy used initial doses of 0.5 mg/kg/day to 1 mg/kg/day, tapered over varying periods of time. The DART study (Dexamethasone: A Randomized Trial) used a lower initial dose of 0.15 mg/kg/day, tapered over 10 days for a cumulative exposure of 0.89 mg/kg, and compared this to placebo.[16] This lower dose facilitated extubation and shortened the duration of intubation for ventilator-dependent infants. Unfortunately, the study was terminated early because of declining enrolment and, although there was no significant difference in death or major disability at follow-up, the study did not have sufficient power to detect differences in long-term outcomes.[17] Several small trials have compared high- to low-dose dexamethasone and have not demonstrated significant dif-
ferences in effects between the doses.\textsuperscript{181-200} A meta-analysis of randomized trials that compared higher versus lower cumulative dexamethasone dosing regimens concluded that there was insufficient evidence to determine an optimal dexamethasone dosing regime.\textsuperscript{211} A systematic review designed to determine whether death as well as pulmonary and neurodevelopmental sequelae were modified by cumulative dexamethasone dosage concluded that higher doses were more effective in reducing the risk of mortality and BPD, but that lower dosage was not associated with a reduction in neurodevelopmental sequelae.\textsuperscript{221} At present, there is insufficient evidence to demonstrate the safety of routine low-dose dexamethasone use.

**Infants at high risk of chronic lung disease**

Oxygen dependency at 36 weeks’ PMA has been shown to be one of three independent predictors of poor neurodevelopmental outcome at 18 to 24 months.\textsuperscript{212} Clinicians therefore have wondered whether postnatal corticosteroids may be justified specifically for infants who are ventilator-dependent and at high risk of CLD. Doyle et al performed a meta-regression of 14 studies and found that the higher the rate of CLD in the control group, the smaller the difference in the rate of death or cerebral palsy between the control and dexamethasone-treated groups.\textsuperscript{231} If the rate of CLD was >65%, dexamethasone treatment appeared to decrease the rate of death or cerebral palsy. This suggests that dexamethasone may be beneficial to infants at very high risk of CLD but this has not yet been studied in clinical trials (Level 5 evidence).

**Hydrocortisone**

Hydrocortisone has been proposed as an alternative to dexamethasone because it is a less potent glucocorticoid and some have speculated that it may have fewer side effects. Furthermore, in addition to anti-inflammatory actions, hydrocortisone may mitigate against adrenal insufficiency experienced by some preterm infants and, thus, decrease the incidence of CLD. Several clinical trials have explored the role of hydrocortisone in preventing CLD and these are summarized in a systematic review that included eight trials enrolling a total of 880 infants.\textsuperscript{241} In all studies, hydrocortisone was started during the first week of life. The initial trial used a high dose of hydrocortisone (15 mg/kg) given two times only; the other trials used initial doses of 1 mg/kg/day to 2 mg/kg/day continued for five to 15 days. In two trials, the primary aim was management of hypotension rather than the prevention or treatment of CLD. Two trials were stopped early because of increased incidence of gastrointestinal perforation in the treatment group.\textsuperscript{251,261} Overall, hydrocortisone therapy did not decrease mortality, the need for oxygen at 36 weeks’ PMA, combined outcome of death or CLD, percent of survivors discharged home on oxygen, or the rate of failure to extubate. Follow-up data from five trials showed no significant difference in the rate of cerebral palsy or of combined mortality and cerebral palsy between hydrocortisone and a placebo.

There have been no randomized trials examining the effect of hydrocortisone given after the first week of life or used to treat infants with prolonged ventilator dependence. One retrospective cohort study compared infants who required assisted ventilation and oxygen after the first one to two weeks of age and received hydrocortisone with a group of healthier infants who did not receive hydrocortisone.\textsuperscript{271} Infants treated with hydrocortisone experienced decreasing oxygen requirements and were successfully weaned from assisted ventilation. After seven days of treatment, there were no differences in oxygen requirements between the two groups. On follow-up, there were no differences in head circumference, neurologic outcome, psychomotor development or school performance. Magnetic resonance imaging performed at eight years of age on a similar cohort of infants treated with hydrocortisone showed that although, overall, children born preterm had significantly reduced grey matter volumes compared to term children, there were no differences in the intracranial volumes, grey matter volumes or white matter volumes between children who did and did not receive hydrocortisone for treatment of CLD.\textsuperscript{281} There were also no differences in neurocognitive outcomes, assessed using the Wechsler Intelligence Scales for Children.

Overall, although hydrocortisone may be a promising alternative to dexamethasone for treating babies with CLD or prolonged ventilator dependence, there is no evidence at this time to show that it is effective or safe.

**Inhaled corticosteroids**

Inhaled corticosteroids have less systemic absorption than systemic corticosteroids and their use has been suggested as a strategy to minimize the short- and long-term adverse effects of systemic corticosteroids. A meta-analysis by V Shah et al, updated in 2007, examined the impact of inhaled corticosteroid therapy started within the first two weeks of life for ventilated preterm neonates on preventing CLD, and concluded that there
was no evidence of reduced CLD. The seven trials used a variety of inhaled corticosteroids (beclomethasone, fluticasone, budesonide, flunisolide) for approximately two to four weeks. Compared to placebo, there were no differences in CLD at 36 weeks’ PMA, death by 36 weeks PMA, death or CLD at 36 weeks, as well as no differences in side effects, including hyperglycemia, hypertension and infection.

Inhaled corticosteroids have also been used in the treatment of infants who remain oxygen and/or ventilator-dependent. The effect of inhaled versus systemic corticosteroids given to ventilator-dependent preterm neonates was examined in a meta-analysis by S Shah. Neither inhaled budesonide nor beclomethasone was more effective than dexamethasone in decreasing death, CLD or the two combined at 36 weeks’ PMA. There were no differences in duration of mechanical ventilation or side-effects. Similarly, two trials that enrolled infants who were oxygen—but not ventilator—dependent and compared inhaled to systemic corticosteroids failed to show significant differences in longer term respiratory outcomes, although the Dimitriou study reported that systemic corticosteroids had a more rapid onset of action and the Nicholl study reported better growth following inhaled corticosteroids. While inhaled corticosteroids likely improve pulmonary mechanics in the short-term, their effect on inflammatory mediators is inconsistent. There are no trials that compare inhaled corticosteroids to placebo for the treatment of CLD, and no systematic follow-up studies of infants who have received inhaled corticosteroids.

There is currently little evidence to support the routine use of inhaled corticosteroids for the prevention or treatment of CLD (Level 1 evidence). Inhaled corticosteroids do not appear to offer significant benefits over systemic corticosteroids for the treatment of infants who remain ventilator-dependent (Level 1 evidence).

Adrenal insufficiency

Preterm newborns may experience relative adrenal insufficiency. Treatment with postnatal corticosteroids may suppress the hypothalamic-pituitary-adrenal axis and further exacerbate this adrenal insufficiency. Although one study reported that a 14-day course of low-dose dexamethasone did not suppress the response to ACTH stimulation compared to placebo, the preterm infants in the study were relatively stable. Clinicians should be aware of the possibility of adrenal suppression in infants who are treated with corticosteroids, particularly if the infant is experiencing stress such as surgery, sepsis or necrotizing enterocolitis.

Recommendations

Based on available evidence:

1. Using postnatal corticosteroids – dexamethasone, hydrocortisone or inhaled corticosteroids – within the first seven days of life to prevent CLD is not recommended. (Grade A recommendation)
2. Administering high-dose dexamethasone (0.5 mg/kg/day) to prevent or treat CLD is not recommended. (Grade A recommendation)
3. The routine use of low-dose dexamethasone (0.15 mg/kg/day to 0.2 mg/kg/day) for all infants who require assisted ventilation after seven days of age to prevent or treat CLD is not recommended. (Grade A recommendation)
4. Hydrocortisone is not recommended for treating CLD. (Grade A recommendation)
5. The routine use of inhaled corticosteroids to prevent CLD is not recommended. (Grade A recommendation)
6. It is unclear whether the benefits of late dexamethasone therapy outweigh the adverse effects for infants who are at high risk of CLD or for those with prolonged ventilator-dependence. If clinicians choose, after parental agreement, to treat an infant who is ventilator-dependent, at risk of severe CLD or who has severe CLD, low-dose dexamethasone (initial dose 0.15 mg/kg/day to 0.2 mg/kg/day) should be used in tapering doses over a short course (seven to 10 days). Inhaled corticosteroids may be considered as an alternative to dexamethasone, but the most effective dose and duration of therapy is not known. (Grade C recommendation)
7. Randomized trials are needed to investigate low-dose dexamethasone treatment regimes, the treatment of infants at high risk for CLD, and the impact of inhaled corticosteroids for the management of infants with CLD. It is imperative that all trials include long-term neurodevelopmental follow-up.
Levels of evidence and strength of recommendations are based on the methods of Canadian Task Force on Preventive Health (see Table 1) [10]: www.canadiantaskforce.ca

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Principal author: Ann L Jefferies MD

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