Are postnatal steroids ever justified to treat severe bronchopulmonary dysplasia?

Eric C Eichenwald, Ann R Stark

Current evidence does not favour use of corticosteroids as neurological side effects may outweigh the benefits of treatment, except perhaps in critically ill infants with respiratory failure

Numerous trials have confirmed that prenatal glucocorticoid treatment of women threatening preterm delivery increases survival and reduces the occurrence of respiratory distress syndrome, intraventricular haemorrhage and necrotising enterocolitis in infants born before 32–34 weeks' gestation.¹ However, despite widespread use of prenatal steroids and administration of surfactant to treat or prevent respiratory distress syndrome, extremely preterm infants remain at high risk for the development of bronchopulmonary dysplasia (BPD). In two large databases in the USA and Canada, BPD, defined as receipt of supplemental oxygen at 36 weeks' postmenstrual age, affected about a quarter of very low birthweight infants, approximately a third of infants weighing 750–1000 g and half of those who weighed less than 750 g at birth.^{2,3}

The cause of BPD in susceptible infants is multifactorial. The immature lung is most vulnerable to disruption of alveolar development in the stage before alveolar formation begins (23–26 weeks' gestation). Factors that increase inflammation in the lung—such as oxygen toxicity, mechanical ventilation-induced trauma from volume and pressure changes, and infection—are associated with the development of BPD. Exposure to chorioamnionitis, with resultant fetal

inflammatory syndrome and high levels of circulating proinflammatory cytokines, also places preterm infants at increased risk of BPD.^{4,5} These data suggest that inflammation has an important role in the pathogenesis of BPD and that the pharmacological modulation of the inflammatory response may be protective.

SHORT-TERM EFFECTS OF POSTNATAL STEROIDS

Observations in the late 1980s suggested that pharmacological doses of corticosteroids (predominantly dexamethasone) given to ventilator-dependent premature infants acutely improved respiratory mechanics and facilitated weaning from mechanical ventilation. Although the numerous randomised controlled trials of corticosteroids to treat or prevent BPD make this one of the most studied treatments in neonatal medicine,^{6–8} the role, if any, of postnatal corticosteroids in the treatment of preterm infants at risk for BPD remains uncertain and controversial. These trials have studied initiation of treatment at ages ranging from shortly after birth to 6 weeks of age, and used different doses and durations of treatment.

Cochrane systematic reviews and meta-analyses of 39 randomised controlled trials of glucocorticoids for the treatment or prevention of BPD are grouped according

to the time of treatment initiation.^{9–11} These meta-analyses have shown improvement in lung function, facilitating earlier extubation, and a decreased rate of BPD when the treatment is given early (<96 h),⁹ moderately early (7–14 days of age)¹⁰ or is delayed (after 3 weeks of age).¹¹ In addition, a decrease in the combined endpoint of mortality or BPD was observed for the moderately early and delayed treatment regimens, although none of the treatment protocols showed improved long-term survival with steroid treatment (table 1). Almost all of these trials used dexamethasone, and most used high doses for long periods of time. These studies may have underestimated the effects of postnatal steroids on lung function because a substantial proportion (in some studies, more than half) of control infants received corticosteroids during or after the formal study protocol.

In many infants in these trials, the known short-term adverse effects of corticosteroids accompanied any improvement in pulmonary function. These complications included hyperglycaemia requiring insulin treatment, hypertension, gastrointestinal bleeding and perforation, an increased risk of infection, hypertrophic cardiomyopathy and decreased somatic and head growth.^{9–11} Despite these short-term adverse effects and the lack of data to support long-term improved survival, the often dramatic effect of dexamethasone therapy on lung function, and its facilitation of earlier extubation, led to its widespread use. From 1996 to 1998, when usage peaked, approximately 25% of all very low birthweight infants admitted to Vermont Oxford Network neonatal units received postnatal steroids (fig 1).¹²

NEURODEVELOPMENTAL FOLLOW-UP

BPD adds to the high risk of cognitive, motor and behavioural impairment in very preterm infants,¹³ and administration of corticosteroids may augment this risk. The recognised adverse effects of experimental administration of perinatal corticosteroids on the central nervous system make this biologically plausible in infants. By the late 1990s, data on longer-term follow-up of infants given glucocorticoids in randomised trials began to diminish enthusiasm for this treatment. Several investigators reported a higher occurrence of cerebral palsy and neurodevelopmental handicap at 18 months and beyond in infants given corticosteroids to prevent or treat established BPD compared with those who received placebo.^{14–18}

Unfortunately, knowledge of long-term outcomes is limited because relatively few

Table 1 Effects of postnatal corticosteroids on respiratory outcome, mortality and neurodevelopment

Outcome	Time of initiation of corticosteroid course		
	Early	Moderately early	Delayed
BPD	↓	↓	↓
Death or BPD	↓	↓	↓
Failure to extubate	↓	↓	↓
Mortality at 28 days	No effect	No effect	Not applicable
Mortality by discharge	No effect	No effect	No effect
Neurodevelopment	Worse	No different (?)	↑ CP, ↓ mortality

BPD, bronchopulmonary dysplasia; CP, cerebral palsy.
Adapted from Halliday *et al.*^{9–11}

Figure 1 Postnatal steroid use in very low birthweight infants in the Vermont Oxford Network, 1990–2005. (Adapted from Walsh *et al.*¹²)

studies have report these outcomes, and the sample sizes are small. In studies that do include follow-up, most track participants only up to 18 months to 2 years of age. Definitions of adverse neurodevelopmental outcomes also vary among the studies, limiting the ability to compare results. Contamination of the control group with open-label steroid administration complicates the interpretation of results in follow-up as well as acute outcomes, and leads to underestimation of the true rate of adverse neurodevelopmental outcomes. One systematic review of randomised trials that included neurodevelopmental follow-up estimated that the relative risk for the development of cerebral palsy with steroid treatment compared with controls was 1.26 (95% CI 1.41 to 2.61).¹⁹ However, the relative risk increased to 2.89 (95% CI 1.96 to 4.27) when only those studies in which less than 30% of the control infants were treated with steroids were included; among followed survivors, the rate of occurrence of cerebral palsy was 38% in treated infants and 14% in controls.¹⁹

Worse outcome has also been reported in school-age children who received early postnatal dexamethasone treatment, suggesting that the neurodevelopmental handicap associated with steroid treatment persists through childhood.²⁰ Yeh *et al* evaluated 146 of 159 survivors (of 262 enrolled in the initial study) at approximately 8 years of age.²⁰ Children in the dexamethasone group had a higher rate of neurodevelopmental disabilities, including lower intellectual quotient scores and poorer motor skills than controls. They also had smaller head circumference and were shorter than controls.

POSSIBLE ROLES OF TIMING OF TREATMENT INITIATION AND DOSE

The timing of steroid treatment may affect the occurrence of neurodevelopmental

complications, although this has not been systematically studied.^{9–11 21} A Cochrane review reported that with treatment after 3 weeks of age, decreased mortality balanced a trend towards an increased rate of cerebral palsy in the corticosteroid group such that the combined rate of death or cerebral palsy did not differ between the steroid and control groups.¹¹ There was also no difference in the combined rate of death or major neurosensory disability and the rate of major neurosensory disability alone. There was no evidence of increased adverse neurological outcomes with the moderately early (7–14 days) treatment strategy, although follow-up data are sparse.¹⁰ The rate of neurological complications seems to be highest in the studies using the early steroid (<96 h) strategy; these studies have the most enrolled infants and the highest rate of long-term follow-up.⁹

No analyses have examined the effect of total dose and duration of dexamethasone treatment on long-term outcome, although a higher rate of neurodevelopmental abnormalities compared with control has been observed with high-dose, prolonged courses of steroids and lower-dose shorter courses particularly for the early treatment regimens. Little information is available for lower initial doses, especially started more than a week after birth. In a trial stopped prematurely because of low enrolment, a 10-day tapering course of dexamethasone (initial dose 0.15 mg/kg/day) given to extremely low birthweight, ventilator-dependent infants more than 1 week of age facilitated extubation, reduced ventilator and oxygen requirements and duration of intubation, and showed a trend towards improved survival without apparent complications.⁸

DEXAMETHASONE COMPARED WITH OTHER CORTICOSTEROIDS

Few long-term outcome data exist for treatment with corticosteroids other than

dexamethasone. Dexamethasone, which was used in most of the trials, may be more neurotoxic than other corticosteroids. A report of differences in intracranial abnormalities in preterm infants of mothers who received antenatal treatment with either betamethasone or dexamethasone supports this concept.²² In a retrospective study, antenatal exposure to betamethasone was associated with a lower risk of cystic periventricular leukomalacia than either exposure to dexamethasone or no glucocorticoid. Animal studies also suggest that dexamethasone may be more neurotoxic than other glucocorticoids.²³ Deleterious effects may be due in part to the sulphite preservative used in the parenteral preparation of dexamethasone.²⁴

It is uncertain whether other corticosteroids would confer respiratory benefit with minimal neurodevelopmental risk. In a recent small case-control study, neurodevelopmental outcomes of infants treated with hydrocortisone were similar to the control group, and outcomes in both these groups were better than those of infants in the dexamethasone-treated group.²⁵ Two randomised trials of early replacement hydrocortisone to prevent BPD were stopped prior to full enrolment because of the higher rate of gastrointestinal perforation in the treated group.^{5 26} One of these studies showed a marked decrease in mortality or rate of BPD in the subgroup of infants exposed to chorioamnionitis, but not in the group as a whole.⁵ Ongoing long-term follow-up of infants in this trial should be informative about a potential association of hydrocortisone administration with adverse outcome.

CURRENT USE OF STEROIDS FOR BPD

Owing to concerns about adverse short-term complications, long-term neurodevelopmental effects, and the absence of long-term benefits, the European Association of Perinatal Medicine in 2001 and the American Academy of Pediatrics (AAP) and the Canadian Paediatric Society in 2002 published statements cautioning on the use of postnatal steroids for the prevention or treatment of BPD.^{27 28} The AAP statement concluded that “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”.²⁸ Concurrent with publication of this statement, the use of corticosteroids for the treatment of BPD has fallen from its peak, although the most recent data available indicate treatment is still commonly given in the most preterm infants.^{12 29} Of very low birthweight infants in the Vermont Oxford

Network database in 2004¹² and 2005 (VON Nightingale database, 2007), approximately 8% received postnatal glucocorticoids, about one-third the rate in years of peak use (fig 1).¹² Treated infants were of lower gestational age and birth weight than in previous time periods, suggesting that steroid treatment was reserved primarily for the smallest and sickest infants. Of note, no change in mortality or short-term morbidity has accompanied the recent decreased use of steroids in the Vermont Oxford Network sites,¹² although other recent data suggest that decreased use of postnatal steroids has been temporally associated with an increased rate of BPD.²⁹

ARE STEROIDS JUSTIFIED TO TREAT SEVERE BPD?

Given concerns about adverse neurodevelopmental effects and no demonstrated long-term improvement with dexamethasone treatment, are postnatal steroids ever justified to treat an infant with severe BPD? Data from prevention trials are unequivocal: early, prophylactic dexamethasone exposes infants who may be at low risk of developing BPD to a potentially toxic drug without clear benefit, and they should not be given this drug. Whether later treatment of established BPD with corticosteroids carries the same risk of compromise as earlier administration is less clear. Protracted ventilation in extremely low birthweight infants is associated with increased likelihood of death or disability. A retrospective analysis showed that mortality increased and survival free of disability decreased with longer duration of mechanical ventilation; only 24% of infants who were ventilated for more than 60 days survived without impairment.³⁰ It is uncertain whether corticosteroid treatment to facilitate earlier extubation would improve outcome, because the prolonged need for mechanical ventilation is often a marker for severity of illness.

In assessing the risks and benefits of corticosteroids, one consideration is whether the risk of neurodevelopmental disability following treatment may be influenced by the risk of developing BPD. This was examined in a meta-regression analysis of published trials of postnatal corticosteroids that included long-term follow-up. In this analysis, corticosteroid treatment increased the chance of death or cerebral palsy when the risk of BPD was relatively low (less than 35%). In contrast, when the risk for BPD exceeded 65%, treatment reduced this combined outcome.²¹ One interpretation of this finding is that corticosteroid treatment might improve survival without increasing adverse neurological outcome in infants with prolonged dependence on a ventilator.

Clinicians continue to treat infants with severe lung disease and evolving BPD with glucocorticoids, even in the absence of strong evidence of benefit and some evidence of harm.^{12 29 31} If corticosteroids promote weaning from the ventilator without worsening neurological outcome in the infants at highest risk for BPD, as Doyle's meta-regression analysis suggests,²¹ research should focus on identifying infants at highest risk for developing BPD. In this high-risk population, treatment with glucocorticoids should be studied using the lowest effective dose for the shortest period, and long-term survival without neurodevelopmental impairment should be the primary outcome. Alternatives to dexamethasone, which may be the most toxic of the available glucocorticoids, should be investigated to understand their pharmacokinetics and pharmacological effects. Until these data are available, corticosteroid therapy outside randomised trials should be avoided in most cases.

In the absence of evidence, can postnatal steroids ever be justified? In infants with life-threatening respiratory disease who require substantial ventilatory support and supplemental oxygen (fractional inspired oxygen >0.8), it is reasonable to consider a therapeutic trial of corticosteroid treatment, although it is difficult to give specific recommendations for when or if this is appropriate. Before treatment, the parents should be informed of the potential lifesaving benefit and the uncertain additional risk of neurological injury, and informed consent should be obtained. The appropriate dose is uncertain, although a lower initial dose, such as 0.15 mg/kg/day of dexamethasone,⁸ is probably more prudent than higher doses. The respiratory status of infants who respond to treatment generally improves within two to three days of initiation; it should be discontinued in those who do not respond. If there is an improvement in lung function, the drug should be weaned quickly over 7–10 days with the goal to accomplish extubation during treatment. Although postnatal corticosteroids may have a narrow use in rescue treatment of critically ill infants with respiratory failure, further investigation is needed to tell us when to use them, and how to use them safely.

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Treatment of respiratory failure in preterms

Is nitric oxide effective in preterm infants?

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There is insufficient evidence to support the routine use of inhaled nitric oxide in preterms with respiratory failure

Inhaled nitric oxide is a selective pulmonary vasodilator used to treat neonates with respiratory failure. The first reports of its use were published in 1991 and the Food and Drug Administration (FDA) approved its use in the USA in 1999. However, it has only relatively recently received regulatory approval in Europe for use in hypoxaemic respiratory failure associated with pulmonary hypertension in neonates ≥ 34 weeks' gestation. Inhaled nitric oxide is often used outside the licensed indication (off-label) in preterm neonates.

Three randomised controlled trials investigating the efficacy of inhaled nitric oxide in preterm infants have been published recently.^{1–3} This article reviews the evidence base for the use of inhaled nitric oxide in the preterm population in the light of these new studies.

RATIONALE FOR THE USE OF INHALED NITRIC OXIDE IN PRETERM INFANTS

Inhaled nitric oxide is potentially beneficial in preterm infants for two main reasons. First, it may improve gas exchange in infants with established respiratory failure through enhanced ventilation–perfusion matching and/or a reversal of extrapulmonary shunting resulting in a lowering of respiratory support requirements and hence reduced ventilator and oxygen-induced lung injury.⁴ Second, inhaled nitric oxide has been shown to reduce lung inflammation

and oxidant stress, preserve surfactant function, and promote lung growth and pulmonary vascular development in various laboratory studies and experimental models of bronchopulmonary dysplasia (BPD).^{5–10} These effects of inhaled nitric oxide may potentially attenuate preterm lung injury and therefore reduce the risk or severity of BPD if it is used at an early stage in the disease process.

RECENTLY PUBLISHED RANDOMISED CONTROLLED TRIALS

Kinsella and colleagues randomised 793 preterm infants ≤ 34 weeks' gestation to receive 5 ppm inhaled nitric oxide or nitrogen placebo gas.¹ Infants were eligible for inclusion into the study if they were < 48 h of age and receiving mechanical ventilation, irrespective of the severity of respiratory disease. The median age at trial entry was approximately 30 h, the mean oxygenation index at trial entry of the babies treated with inhaled nitric oxide and controls was 5.4 and 5.8, respectively, and the median duration of gas treatment was 14 days, indicating this was a study investigating the efficacy of early, low-dose, prolonged “prophylactic” inhaled nitric oxide in ventilated preterm infants with mild respiratory disease. Although the overall results showed no evidence of a benefit in the combined primary outcome of death and/or BPD (relative risk (RR) 0.95, 95% CI 0.87 to 1.03), prespecified subgroup analyses

showed that inhaled nitric oxide reduced BPD/death in larger preterm infants with a birth weight of between 1000 g and 1250 g (RR 0.60, 95% CI 0.42 to 0.86). Interestingly, and in line with another study of early prophylactic treatment,¹¹ inhaled nitric oxide reduced the risk of cerebral injury on cranial ultrasound, defined as severe intraventricular haemorrhage (IVH), periventricular leukomalacia (PVL) or ventriculomegaly (RR 0.73, 95% CI 0.55 to 0.98, number needed to treat (NNT) 16); subgroup analysis suggested that this protective effect of inhaled nitric oxide on brain injury was confined to babies with a birth weight of 750–999 g.

In another large, multicentre placebo-controlled randomised controlled trial conducted in the USA, Ballard and colleagues enrolled 582 preterm infants ≤ 32 weeks' gestation receiving nasal continuous positive airway pressure or mechanical ventilation and aged between 7 days and 21 days.² Infants initially received 20 ppm of inhaled nitric oxide for 48–96 h with the dose being weaned thereafter to 10 ppm, 5 ppm and 2 ppm at weekly intervals; gas treatment was continued for a minimum of 24 days (median 25 days). Most of the babies were ventilated but had relatively mild respiratory support requirements and their median age at trial entry was 16 days, indicating this was a study designed to test the efficacy of late inhaled nitric oxide treatment in improving survival without chronic lung disease (CLD) (ie, preventing death/CLD) in preterm babies requiring ongoing respiratory support. Survival without CLD at 36 weeks post-menstrual age was improved in infants treated with inhaled nitric oxide (RR 1.23, 95% CI 1.01 to 1.51; NNT 14). Post hoc analyses indicated that this benefit was evident only in infants aged 7–14 days at randomisation and there was no evidence of an effect on outcome of birth weight or the severity of underlying respiratory disease. Infants treated with inhaled nitric oxide were discharged earlier and received mechanical respiratory support and supplemental oxygen