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Postnatal corticosteroids to prevent or treat bronchopulmonary dysplasia – Who might benefit?

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A B S T R A C T

Newborn infants born very preterm are at high risk of developing bronchopulmonary dysplasia, which is associated with not only mortality but also adverse long-term neurological and respiratory outcomes in survivors. Postnatal corticosteroids might reduce the risk of developing bronchopulmonary dysplasia, or reduce its severity. However, it is important to minimize exposure to the potentially harmful effects of corticosteroids, particularly on the developing brain. Systemic corticosteroids started after the first week of life have shown the most benefit in infants at highest risk of developing bronchopulmonary dysplasia, whereas inhaled corticosteroids have little effect in children with established lung disease. Systemic corticosteroids in the first week of life are not recommended, but inhaled corticosteroids, or corticosteroids instilled into the trachea using surfactant as a vehicle to distribute the corticosteroids through the lungs, offer promise with respect to prevention of bronchopulmonary dysplasia.

1. Introduction

Corticosteroids to prevent or treat bronchopulmonary dysplasia (BPD) are controversial. Because of high rates of adverse outcomes, including gastrointestinal perforation in the short term, and cerebral palsy in the long term, many esteemed bodies, such as the American Pediatric Society, the Canadian Paediatric Society [1], and the European Association of Perinatal Medicine [2], have warned against the routine use of corticosteroids in high-risk infants. Although such warnings have resulted in a reduction in prescribing, corticosteroids remain a common treatment in very preterm infants, partly because BPD itself is associated with adverse long-term neurological and respiratory outcomes, and there are no alternative therapies known to be as effective in facilitating extubation in preterm children with severe lung disease. Clearly clinicians need guidance in balancing the risks versus benefits of corticosteroids in high-risk infants.

Corticosteroids could be administered either directly to the lung via the tracheobronchial tree, or indirectly via the bloodstream, through either parenteral or enteral administration. Direct administration to the lung is intuitively sensible, as it would limit exposure of non-lung organs to the potential harmful effects of corticosteroids. Corticosteroids can be aerosolized and added to the air the baby is breathing, but only a small proportion of the drug eventually reaches the lung. To overcome the problem of poor delivery of the drug, an alternative method is to add the corticosteroid to exogenous surfactant, then inject the combination into the trachea.

Regardless of the mode of administration, it is important to know that the nett benefits of treatment with corticosteroids to prevent or treat BPD exceed the nett harms. The purpose of this review is to weigh the evidence for and against corticosteroids after birth to prevent or treat BPD. We consider different ways of administering corticosteroids, including inhaled, intratracheal, and systemic. Evidence from randomized controlled trials (RCTs), and syntheses of RCTs are relied upon the most to form our views. Although BPD is the major outcome of interest in this review, we consider competing risks of death, as well as other possible harms, including short-term complications and adverse long-term neurological sequelae, such as cerebral palsy.

2. Inhaled corticosteroids

There are two reviews in the Cochrane Library on the topic of

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inhaled corticosteroids; one on early use to prevent BPD [3], and the other considers trials when lung disease is more established [4].

2.1. Early inhaled corticosteroids

Shah et al. [3] synthesized the evidence concerning early (<2 weeks after birth) inhaled corticosteroids. For the outcome of death or BPD at 36 weeks, there were six trials that recruited 1285 participants. Fewer infants in the inhaled corticosteroid group had either died or had BPD at 36 weeks than controls: 35% (227/649) vs 40% (256/636), respectively [risk ratio (RR): 0.86; 95% confidence interval (CI): 0.75, 0.99; $P = 0.04$]. In the inhaled corticosteroid group, there were fewer survivors with BPD at 36 weeks: 24% (131/544) vs 31% (171/554), respectively (RR: 0.76; 95% CI: 0.63, 0.93; $P = 0.005$). There were no obvious differences between inhaled corticosteroid and comparison groups for complications such as patent ductus arteriosus (PDA), hyperglycemia, hypertension, sepsis, or gastrointestinal bleeding.

The results of the systematic review are dominated by the trial of Bassler et al. [5]; prior to the inclusion of the Bassler et al. study there was little evidence of any effects of inhaled corticosteroids [6]. Bassler et al. recruited 863 infants born 23–27 weeks gestation who at <12 h required positive pressure support. Infants were randomly allocated to either budesonide or placebo, delivered via a spacer. The dose of budesonide was 400 μg 12-hourly for 14 days, then 200 μg 12-hourly until either 32 weeks postmenstrual age, or they were off respiratory support. In their study 40% (175/437) of infants in the budesonide group had died or had BPD by 36 weeks compared with 46% (194/419) in the placebo group (RR: 0.86; 95% CI: 0.75, 1.00; $P = 0.05$). Interestingly, the improvement was influenced by a substantial reduction in the rate of BPD [budesonide 28% (101/363) vs placebo 38% (138/363); RR: 0.74; 95% CI: 0.60, 0.91; $P = 0.004$] at the expense of a small increase in mortality by 36 weeks (17% (74/437) budesonide vs 14% (57/419) placebo; RR: 1.24; 95% CI: 0.91, 1.69); $P = 0.17$). Moreover, approximately two-thirds of the infants enrolled were intubated and ventilated at trial entry, among whom there was less effect of inhaled budesonide on the outcome of death or BPD (49% budesonide group vs 51% control), whereas among the remaining one-third who were not intubated on entry to the trial, there was a larger effect of inhaled budesonide on the outcome of death or BPD (21% budesonide group vs 36% control). This discrepancy does not make clinical sense, unless it suggests that the intubated babies had more established lung disease and that too much damage had already occurred to the lung prior to starting the inhaled corticosteroids. Bassler et al. also reported some other benefits for inhaled budesonide, including lower rates of PDA and reintubation. Interestingly almost one-third in both groups ultimately received systemic corticosteroids (29% budesonide vs 32% controls). Follow-up of the cohort is in progress, and may help to understand the effect of inhaled corticosteroids on the balance between the competing risks of death and BPD.

Long-term outcomes have been reported for two trials in the systematic review; there was little evidence of effects of inhaled corticosteroids on rates of neurodevelopmental impairment or readmission to hospital for respiratory illnesses [7,8].

2.2. Later inhaled corticosteroids

Onland et al. [4] reviewed the evidence concerning later inhaled (≥7 days after birth) corticosteroids. There were not many trials ($n = 8$) or participants ($n = 232$) overall, and few studies reported important outcomes such as mortality or BPD, and hence there is little evidence on which to make any clinical recommendations concerning inhaled corticosteroids in infants with established lung disease.

3. Intratracheal administration of corticosteroids

There is only one RCT that has assessed intratracheal administration of corticosteroids. Yeh et al. [9] recruited 265 infants with birthweight <1500 g, with a chest X-ray consistent with severe respiratory distress syndrome, and who were intubated and ventilated, requiring ≥50% oxygen, and who were <4 h after birth. Infants were randomly allocated to budesonide 0.25 mg/kg mixed with 100 mg/kg surfactant or to surfactant only. The surfactant was Survanta® (AbbVie, Inc., North Chicago, IL, USA). Doses of study medication were given every 8 h until the oxygen requirement was <30%. Death or BPD at 36 weeks was less frequent in the budesonide group (42%; 55/131) than in the controls (66%; 89/134) (RR: 0.58; 95% CI: 0.44, 0.77; $P < 0.001$). The rates of BPD alone at 36 weeks were 29% (38/131) in the budesonide group vs 50% (67/134) in the control group (RR: 0.70; 95% CI: 0.58, 0.86; $P < 0.001$), whereas death alone at 36 weeks was not reduced as much: 13% (17/131) budesonide vs 16% (22/134) controls (RR: 0.96; 95% CI: 0.87, 1.06; $P = 0.54$). Follow-up of survivors to 30 months of age is in progress, but thus far there have been no substantial differences observed in rates of neurosensory impairment or in Bayley Scale scores [9]. This study has treatment effects that are large and would be very important if replicated.

4. Systemic corticosteroids

There are two Cochrane reviews in which systemic corticosteroids are compared with controls, one focusing on treatment starting early (<8 days of age) [10], the other in which treatment starts later (>7 days of age) [11].

4.1. Early (<8 days of age) systemic corticosteroids

Of the corticosteroids available for systemic treatment, randomized trials have only been reported where dexamethasone or hydrocortisone were the primary drugs of interest. There are 20 early randomized controlled trials in which outcomes in infants treated with dexamethasone have been compared with controls, and nine trials in which infants treated with hydrocortisone have been compared with controls [10].

4.1.1. Early dexamethasone

There are numerous benefits from early dexamethasone, including lower rates of BPD at both 28 days and 36 weeks, and regarding the combined outcomes of BPD at both ages with death, lower rates of failure to extubate, PDA and retinopathy of prematurity (ROP), and less need for later systemic corticosteroids (Table 1). These benefits are counteracted by a number of harms, most notably more gastrointestinal perforation in the short term, and more cerebral palsy in the long term (Table 1). On balance, the benefits of systemic dexamethasone starting in the first week of life do not outweigh the harms, particularly cerebral palsy, and dexamethasone in the first week of life is not recommended to prevent BPD.

4.1.2. Early hydrocortisone

In the Cochrane review there are few effects of early hydrocortisone in the doses used in the RCTs [10]. However, since the Cochrane review was published in 2014 there has been a large randomized trial of early hydrocortisone reported by Baud et al., 2016 [12]. They recruited 523 inborn infants 24–27 weeks gestation in the first 24 h after birth who were considered likely to survive the immediate newborn period. Infants were randomly allocated to either 8.5 mg/kg of hydrocortisone or placebo for a total of 10 days. Of the infants treated with hydrocortisone, 60% (153/

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