Perinatal prevention of bronchopulmonary dysplasia

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Abstract

Bronchopulmonary dysplasia (BPD), defined as oxygen dependency for at least 28 days after birth, is a common adverse outcome of very premature birth. Affected children require frequent readmissions to hospital in the first 2 years, and although lung growth and remodelling results in progressive improvement in lung function, airflow abnormalities may remain. Indeed, the most severely affected experience troublesome respiratory symptoms as adolescents and young adults. As a consequence, many potential preventative strategies have been investigated, and some have resulted in a reduction in BPD but with a negative risk/benefit ratio, for example, postnatal corticosteroids. Others therapies, namely antenatal corticosteroids and postnatal surfactant, have resulted in significant benefits to infants, including reductions in respiratory distress syndrome, necrotising enterocolitis, intraventricular haemorrhage and neonatal death, but have not impacted favourably on the incidence of BPD, perhaps due to the increased survival of very immature infants. In one major trial, it has been shown that BPD can be reduced without adverse effects by caffeine administration. Avoidance of high oxygen concentrations at resuscitation is also a promising approach to reduce BPD.

Keywords: Bronchopulmonary dysplasia; corticosteroids; methylxanthines; resuscitation; surfactant.

Introduction

Bronchopulmonary dysplasia (BPD) is a common adverse outcome of neonatal intensive care, particularly in infants born very prematurely [42]. Various criteria have been used to diagnose BPD, but currently, infants are usually diagnosed as having BPD if they had been oxygen dependent for at least 28 days after birth. Prematurely born infants are then classified as having mild, moderate or severe BPD according to their respiratory support requirement at 36 weeks post-menstrual age (PMA) [41]. To enable a more accurate diagnosis, an oxygen reduction test is used to determine whether supplementary oxygen is still required [91].

Children who have had BPD can require supplementary oxygen at home for many months or even years, but few remain oxygen dependent beyond 2 years [27]. They have frequent readmissions to hospital in the first 2 years after birth, particularly if they have a respiratory syncytial virus lower respiratory tract infection [29] or required supplementary oxygen at home [28]. Many experience troublesome, chronic respiratory symptoms requiring treatment and have lung function abnormalities. In the first 2 years, children with BPD have high airways resistance, gas trapping and ventilation inhomogeneity and, although lung growth and remodelling results in progressive improvement in lung function [6], airflow abnormalities may remain [25]. The most severely affected have lung function abnormalities and troublesome respiratory symptoms as adolescents and young adults [47, 58]; one study demonstrated that females rather than males may be more affected [90].

BPD has a multifactorial aetiology. Infants, in the past, developed BPD after severe respiratory failure, frequently compounded by the development of a patent ductus arteriosus (PDA), pulmonary interstitial emphysema and/or infection, necessitating high-pressure ventilation and supplementary oxygen concentrations. The so-called new BPD, however, occurs in very prematurely born infants who initially had minimal or even no signs of lung disease [66]. Affected infants also experience respiratory morbidity at follow-up [31]. It therefore remains important to prevent BPD. The aim of this review was to evaluate the literature to identify whether there are effective strategies to prevent BPD that have a positive risk/benefit ratio.

Antenatal

Corticosteroids

Corticosteroids are given antenatally to women at risk of premature delivery with the aim of maturing their infant’s lungs and hence reducing the likelihood of respiratory distress syndrome (RDS) and associated complications. Indeed, a meta-analysis of the results of 21 randomised controlled
trials (RCTs), including 4629 infants, highlighted significant benefits to infants, including reductions in RDS, necrotising enterocolitis (NEC), intraventricular haemorrhage (IVH) and neonatal death but not in BPD [64]. There were no adverse effects to the mothers with regard to death, sepsis or chorioamnionitis, and corticosteroids were equally effective in women with prolonged rupture of the membranes or pregnancy-related hypertension [64]. There are, however, concerns regarding the effect of corticosteroids on brain and lung growth, as animal models treated have fewer and larger alveoli [94]. As a consequence, repeated courses are not recommended. In addition, there are differences in the effects of the different steroids; a meta-analysis of ten RCTs highlighted that dexamethasone compared with betamethasone was associated with less IVH [14].

**Thyroid-releasing hormone**

Thyroid-releasing hormone (TRH) given antenatally has not been demonstrated to reduce BPD in large randomised trials [19].

**Antioxidants**

Oxidative stress has been implicated in the development of BPD, and the antioxidant defences of prematurely born infants are impaired. High-dose antenatal vitamin C and E supplementation in women at risk of pre-eclampsia, however, did not improve infant respiratory outcome and indeed was associated with increased health-care utilisation and related cost of care [32].

**Postnatal**

**Resuscitation**

In the majority of UK hospitals with neonatal intensive care units, prematurely born infants are initially resuscitated using air [56], this is to reduce the likelihood of oxygen toxicity. Indeed, in an RCT of infants born between 24 and 28 weeks of gestation, resuscitation with 30% rather than 90% oxygen was associated with a lower incidence of BPD at hospital discharge and fewer days of both supplementary oxygen and mechanical ventilation [89].

**Surfactant**

RDS results from surfactant deficiency, and it has been well shown that surfactant administration after birth reduces RDS. Administration of synthetic or animal-derived surfactants has been shown in placebo controlled trials to have many benefits, but not a reduction in BPD, possibly because of the increased survival of very prematurely born infants following surfactant administration. A meta-analysis of 11 RCTs demonstrated a greater efficacy of animal-derived surfactants compared with synthetic surfactants, with a greater reduction in pneumothorax and mortality [80]. The likely explanation for the greater benefit of the animal-derived surfactants is that they contain surfactant proteins. As a consequence, synthetic surfactants have been developed, which contain proteins mimicking the functions of surfactant proteins. Lucinactant contains a 21-residue synthetic peptide that mimics the functions of surfactant protein B, and in two RCTs, it performed similarly to animal-derived surfactants [63]. Later dosing at 3 to 10 days with one or two doses of lucinactant compared with placebo, however, did not significantly reduce BPD [49].

Amongst infants with established RDS, multiple doses, rather a single dose, of an animal-derived surfactant results in greater improvements in oxygenation and ventilatory requirements and a decreased risk of pneumothorax [81]. Early studies suggested that infants given prophylactic rather than selective surfactant had improved clinical outcomes, but a meta-analysis of 11 studies, including those with routine use of continuous positive airway pressure (CPAP) and maternal administration of corticosteroids, failed to confirm an advantage [67]. It should be noted that the majority of the surfactant trials occurred before the routine use of prenatal corticosteroids.

**Inositol**

Inositol promotes the maturation of surfactant phospholipids and the synthesis of phosphatidylinositol, but inositol supplementation in two RCTs did not significantly reduce BPD [39].

**Ventilation strategies**

Baro/volutrauma has been implicated in the development of BPD, and as a consequence, a variety of strategies have been investigated in an attempt to reduce BPD. These include (a) avoidance of intubation and mechanical ventilation by use of CPAP or non-invasive ventilation, (b) synchronised mechanical ventilation with positive pressure inflations and spontaneous inspiration coinciding, with the adequate gas exchange being achieved at lower peak pressures reducing the likelihood of barotrauma, and (c) reduction in excessive volume delivery, thus reducing the likelihood of volutrauma, using either volume-targeted ventilation (VTV) or high-frequency oscillation (HFO). Observational studies highlighted that the use of early CPAP rather than intubation and ventilation was associated with a lower incidence of BPD, but that effect was not confirmed by a meta-analysis [85] or by the results of three more recently reported large RCTs [55, 71, 86]. A meta-analysis of six RCTs demonstrated that intubation and early surfactant followed by extubation to CPAP compared with later selective surfactant was associated with a lower incidence of mechanical ventilation, air-leak syndromes and BPD [82]. A larger proportion of the early surfactant group, however, received surfactant, which may have accounted for at least some of the beneficial effects [82]. Results from three studies have suggested that weaning from CPAP by pressure reduction rather than time-cycling reduced BPD, but two of the studies have only been reported in abstract form; this strategy...
merits further testing [15]. Non-invasive ventilation, such as synchronised nasal IPPV (SNIPPV), has been investigated with regards to reducing the incidence of BPD. In one study [9], SNIPPV using the Infant Star and Graesby capsule was associated with a significant reduction in the combined outcome of BPD or death ($P=0.02$) and BPD alone ($P=0.03$) in infants with birth weights between 500 and 750 g [9]. There were, however, no such effects in other birth weight groups, and the study was a non-randomised retrospective review [9]. Appropriately designed RCTs are required before meaningful conclusions can be drawn regarding the efficacy of non-invasive ventilation. Physiological studies highlighted many advantages of synchronised ventilation; a meta-analysis of 14 RCTs, however, showed no benefit with regard to BPD, but there were reductions in pneumothorax and the duration of ventilation [30]. During VTV, a preset volume is delivered regardless of the changes in the infant's lung volume. A meta-analysis of the results of 12 RCTs highlighted that VTV compared with pressure-limited ventilation resulted in reductions in the combined outcome of death or BPD, pneumothorax, hypacardia, periventricular leukomalacia (PVL)/grades 3–4 IVH and the duration of ventilation [93]. In certain trials, however, different ventilators were used in the two arms, and a wide range of volume-targeted levels were used, which affects the work of breathing [62]. During HFO, small tidal volumes are delivered at very fast frequencies. A meta-analysis of 17 RCTs demonstrated that the use of HFO was associated with a reduction in BPD, but this was of borderline significance and a variety of oscillators and study designs were used [17]. In the largest RCT (n=797, United Kingdom Oscillation Study, UKOS) [42], infants <29 weeks of gestational age were randomised within 1 h of birth, no acute benefits were demonstrated and, in a subgroup, lung function at 1 year was similar in infants who had been supported by HFO or conventional ventilation [87]. There is, however, some non-randomised evidence suggesting that HFO may protect small airway function [38], which was not assessed in the original UKOS follow-up [87]. As a consequence, the UKOS children are now having comprehensive cardiorespiratory and functional review as school children to determine whether or not HFO in very prematurely born infants has any long-term benefits or adverse effects.

**Anti-inflammatory agents**

**Corticosteroids** Corticosteroids are potent anti-inflammatory agents. There have been numerous RCTs of systemically administered corticosteroids [33–35]. The efficacy of administration within 96 h of birth has been examined in 21 trials; a meta-analysis demonstrated a significant reduction in BPD [33]. Twenty-eight RCTs of postnatal systemic corticosteroid therapy (dexamethasone, n=20, or hydrocortisone, n=8) commenced within the first week after birth were assessed in a Cochrane review [36]. Demonstrated benefits included earlier extubation and significant reductions in BPD at both 28 days and 36 weeks’ PMA, death or BPD both at 28 days and 36 weeks’ PMA, PDA and retinopathy of prematurity (ROP). Adverse effects included gastrointestinal bleeding, intestinal perforation, hyperglycaemia, hypertension, hypertrophic cardiomyopathy and growth failure. There were no significant differences in the rates of mortality, infection, severe IVH, PVL, NEC or pulmonary haemorrhage. Late outcomes were reported from 12 trials and included increases in developmental delay, cerebral palsy and abnormal neurological examination. Subgroup analyses demonstrated that most of the benefits and the adverse effects were related to dexamethasone administration; hydrocortisone had little effect on any outcome, except increasing intestinal perforation. The authors of the Cochrane review concluded that the benefits of corticosteroid administration did not outweigh the adverse effects [36]. Seven trials have investigated the administration between 7 and 14 days and highlighted a significant reduction in BPD and facilitation of extubation [34]. Nine trials investigated the administration after 3 weeks and demonstrated less need for home oxygen and rescue steroid therapy [35]. A meta-analysis of the results of 20 RCTs demonstrated that systemic administration of corticosteroids was associated with a relative risk (RR) for cerebral palsy of 1.45 (95% confidence interval, CI, 1.13–1.87) [24]. Further analysis demonstrated that only early (RR 1.70, 95% CI 1.20–2.42) and not late (RR 1.20, 95% CI 0.83–1.74) treatment was associated with a significant excess of cerebral palsy [24]. In the trials in which corticosteroids were administered later, however, greater crossover occurred, which may have obscured any effect.

To avoid the adverse neurodevelopmental effects of systemic corticosteroids, the efficacy of lower dosage has been explored. In one study, infants of gestational age <28 weeks and birth weight <1000 g, who received dexamethasone 0.89 mg/kg over 10 days rather than placebo, were more likely to be extubated by 10 days (RR 11.2, 95% CI 3.2–39), but there was no significant effect on BPD [23]. Follow-up of the infants did not demonstrate a significant difference in functional outcomes, but the number of infants studied was relatively small. An alternative approach has been to use the inhaled route, but a meta-analysis of the results of 11 RCTs, in which inhaled steroids were given before 2 weeks old, demonstrated no reduction in BPD [77]. In addition, a meta-analysis in which the results of randomised or quasi-randomised trials of inhaled vs. systemic steroids were compared demonstrated that inhaled steroids were associated with longer durations of supplementary oxygen and ventilator dependence [79]. In a pilot RCT, direct instillation of budesonide into the trachea using surfactant as a vehicle resulted in a significant reduction of the combined outcome of death or BPD with no adverse effects on physical growth or neurological outcome [48]. The number of infants included in the study, however, was too small to draw definitive conclusions to inform routine practice.

**Cromolyn sodium** Cromolyn sodium is a mast cell stabiliser that prevents the degranulation and release of histamine and decreases neutrophil migration and activation, but no reduction in BPD was demonstrated in two small RCTs [57].
Macrolides  Macrolide antibiotics have anti-inflammatory actions including inhibiting proinflammatory cytokines, inhibiting inflammatory transcription factors and acting as free radical scavengers. They also directly inhibit neutrophil chemotaxis and inhibit superoxide generation by activated neutrophils. A review of 17 studies demonstrated that the RR of BPD development in babies colonised with Ureaplasma urealyticum was 1.7 [92], but the administration of the macrolide, erythromycin, did not reduce BPD [51]. Azithromycin is a newer-generation macrolide that has fewer side effects and increased anti-inflammatory properties compared with erythromycin. Despite promising results from animal models [3], although azithromycin significantly reduced IL-6 and IL-8 production by tracheal cells obtained from prematurely born infants [1], BPD was not significantly reduced by giving azithromycin for a maximum of 6 weeks [4]. In an RCT, the incidence of BPD was lower in clarithromycin vs. placebo treated infants (2.9% vs. 36.4%) [60], but the proportions of infants receiving prenatal steroids and postnatal surfactant were relatively low, making it difficult to generalise the results.

Fluid restriction, PDA and diuretics

Excessive fluid intake can compromise lung function and increases the risk of PDA and BPD. Nevertheless, fluid restriction, therapeutic duct closure or diuretics have not reduced BPD. A meta-analysis of five RCTs demonstrated restriction, therapeutic duct closure or diuretics have not significantly reduced BPD. A meta-analysis of five RCTs demonstrated that restricted fluid intake was associated with significantly reduced BPD [51]. Azithromycin is a newer-generation macrolide that has fewer side effects and increased anti-inflammatory properties compared with erythromycin. Despite promising results from animal models [3], although azithromycin significantly reduced IL-6 and IL-8 production by tracheal cells obtained from prematurely born infants [1], BPD was not significantly reduced by giving azithromycin for a maximum of 6 weeks [4]. In an RCT, the incidence of BPD was lower in clarithromycin vs. placebo treated infants (2.9% vs. 36.4%) [60], but the proportions of infants receiving prenatal steroids and postnatal surfactant were relatively low, making it difficult to generalise the results.

Vitamin A

Vitamin A is required in the fetal lung for both cellular differentiation and surfactant synthesis. Prematurely born infants are frequently deficient in vitamin A because of the deprivation of transplacental acquisition, which mainly occurs in the third trimester. A meta-analysis of the results of eight RCTs demonstrated that vitamin A supplementation was associated with a significant reduction in oxygen requirement at 36 weeks’ PMA, but the effect was modest and confined to infants with a birth weight <1000 g [20]. There were no other proven benefits from repeated intramuscular injections [20], and toxic levels of vitamin A can cause non-specific neurological signs and vomiting due to raised intracranial pressure, although these have not been reported to occur in the RCTs. The optimum dosage regimen and route of administration, therefore, require further study.

Antioxidants

The results of postnatal antioxidant administration with regard to BPD development have been mixed. Animal and human studies demonstrated that acute and chronic lung injury secondary to hyperoxia can be reduced by the administration of superoxide dismutase (SOD) [22, 61]. In an RCT, however, prophylactic supplementation with recombinant human CuZnSOD resulted in fewer episodes of respiratory illness (wheezing, asthma, pulmonary infections) severe enough to require treatment with bronchodilators or corticosteroids at 1 year corrected age, but there was no reduction in BPD [21]. Glutathione is an endogenous scavenger of free radicals, and the immature lung is deficient in glutathione synthesis [40]. Synthesis of glutathione is limited by the availability of cysteine. Yet in a multicentre RCT [2] of 391 infants with birth weight <1000 g, no significant differences were found in the incidence or severity of BPD between those who received N-acetyl cysteine (NAC) for 6 days or placebo. A possible explanation for the lack of a positive effect was that NAC was started when the infants were 36 h of age, which might be too late, given the immediate postnatal oxygen radical surge [70]. Allopurinol is a free radical scavenger and synthetic inhibitor of xanthine oxidase, which generates superoxide radicals following hypoxia. Nevertheless, in an RCT of 400 infants born between 24 and 32 weeks of gestation, allopurinol given enterally did not significantly reduce BPD [69]. Melatonin is a potent free radical scavenger [65], and in an RCT, melatonin administration was associated with significantly lower levels of proinflammatory cytokines and reduced ventilatory requirements during the perinatal period [26], but whether it reduces BPD requires testing. Although vitamin E is a scavenger of free radicals, a meta-analysis of the results of four randomised studies demonstrated that vitamin E supplementation did not significantly affect the risk of BPD [10], and a review of 26 trials highlighted that high-dose, intravenously administered vitamin E increased the risk of sepsis [10]. Cimetidine is a cytochrome P450 (CYP) inhibitor and prevents pulmonary gas exchange failure in newborn lambs after breathing 95% oxygen for 72 h [37]. In an RCT of 84 newborns weighing <1251 g, however, cimetidine compared with placebo had no significant effects on the severity of respiratory insufficiency assessed at 10 days postnatal age [18]. Infants who develop BPD have a 20-fold increase in the neutrophil influx [54] and an imbalance between proteases and antiproteases [83]. A low functional level of α1-protease inhibitor at birth may predict BPD development [68], but in an RCT of neonates aged <24 h, with birth weights between 600 and 1000 g, and requiring respiratory support or with birth weight between 1001 and 1250 g and with RDS, supplementation did not result in a significant reduction in BPD, but there was a lower incidence of pulmonary haemorrhage [83].

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Methylxanthines

Methylxanthines are phosphodiesterase inhibitors. They facilitate extubation and reduce apnoea, but there have been concerns regarding their potential harmful effects due to their inhibition of adenosine receptors. Adenosine preserves brain ATP levels and protects the brain cells during experimental hypoxia and ischaemia. Fortunately, in a large RCT of 2006 infants with birth weights between 500 and 1250 g who required respiratory stimulants for apnoea or to facilitate extubation during the first 10 days after birth, there was no increase in cerebral palsy, but rather caffeine administration was associated with a reduction in cerebral palsy (odds ratio, OR, 0.58, 95% CI 0.39–0.87) at a corrected age between 18 and 21 months [74]. In addition, caffeine administration was associated with a significant reduction in BPD (OR 0.63, 95% CI 0.52–0.78) [73]; the lung-protective effect of caffeine may have resulted from a decreased need for PDA closure.

Pentoxifylline is a non-selective phosphodiesterase inhibitor and has anti-inflammatory effects that decrease neutrophil sequestration and inhibit neutrophil-derived oxidation production. In an RCT [50] of 150 very-low-birth-weight infants, who all needed supplementary oxygen on the fourth day after birth, pentoxifylline administration compared with placebo was associated with a significant reduction in BPD development (OR 0.32, 95% CI 0.11–0.94). Only 97 of the randomised 150 infants, however, were included in the analysis; subject “dropout” was due to deaths or withdrawal of consent. Further studies are required to assess this preventative strategy.

Oestradiol and progesterone

Oestradiol and progesterone are important in lung growth. Ovariectomy in a female rat model reduces the gas exchange surface area by impaired formation of alveoli [52], and treatment of pig fetuses with oestrogen and progesterone receptor antagonists impairs alveolar formation [88]. In an RCT of 83 infants <29 weeks of gestation, the replacement hormones given for at least 2 weeks did not reduce the combined outcome of BPD or death (48% vs. 44%), but the risk of BPD was inversely proportional to the length of administration [88]. This strategy merits testing in larger studies.

Thyroxine

In two RCTs, postnatal thyroxine administration failed to reduce the severity of RDS, neonatal morbidity or neonatal mortality [59].

Nitric oxide

Nitric oxide (NO) is a potent pulmonary vasodilator, and if given by inhalation (iNO), it selectively decreases pulmonary vascular resistance, thus improving oxygenation. Hence, it was proposed that iNO might prevent BPD development by reducing the need for a high oxygen concentration and ventilatory support level. A meta-analysis of the results of six RCTs [7], however, demonstrated that iNO given as early rescue therapy in the first 3 days after birth resulted in no significant effect on BPD or mortality [7]. In only one multicentre trial [45] included in the meta-analysis, in which infants received 5 ppm of iNO or placebo for 21 days or until extubation, there was a reduction in BPD, which was in infants with a birth weight of 1000–1250 g. In a single-centre study that included 207 infants <72 h of age requiring ongoing ventilation, the routine use of iNO at a starting dose of 10 ppm was associated with a significant reduction in the combined outcome of death or BPD and also in intracranial haemorrhage or PVL [75]. A meta-analysis of the two studies in which iNO was used routinely for intubated preterm infants, however, demonstrated a barely significant reduction in the incidence of the combined outcome of death or BPD (RR 0.91, 95% CI 0.84–0.99) [7]. In two studies, iNO was given later, that is, after 3 days of age to infants considered at increased risk of BPD [5, 84]; neither showed a reduction in BPD, but a modest effect was shown in one [5] on subanalysis. NO also promotes cell and vessel growth in the immature lung [44] and has anti-inflammatory effects; low-dose iNO decreases lung neutrophil accumulation [46]. Nevertheless, in a multicentre RCT, low-dose, prophylactic use of iNO did not reduce BPD or any other adverse outcome [53]. An aim of that trial had been to investigate prolonged administration of iNO, which meant certain infants received iNO after extubation, and whether that influenced the results merits consideration. Nevertheless, a recent meta-analysis of 12 RCTs, which included prematurely born infants, demonstrated no significant effect of iNO on BPD or death or severe neurological events on imaging [45]. The NIH Consensus Development Conference statement on iNO therapy for premature babies [76] considered 14 RCTs of iNO treatment in premature infants of ≤34 weeks of gestation and highlighted equivocal effects on pulmonary outcomes, survival and neurodevelopmental outcomes. They [76] concluded that the available evidence does not support use of iNO in early routine, early rescue or later rescue regimens in the case of premature infants <34 weeks of gestation who require respiratory support.

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