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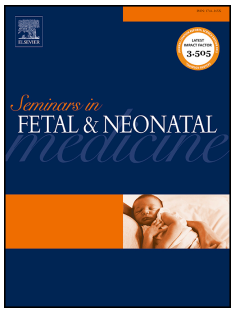

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Alternatives to systemic postnatal corticosteroids: inhaled, nebulized and intratracheal

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ABSTRACT

Concern about adverse outcomes with the use of systemic postnatal corticosteroids (PCS) for bronchopulmonary dysplasia (BPD) have led to the widespread use of alternative methods of administration in research and clinical care. Theoretically, administration of topical (directly to the lung) corticosteroids may allow for beneficial effects on the pulmonary system with a lower risk of undesirable side effects compared with systemic administration. Current evidence suggests that inhaled corticosteroids may be an effective therapy in the management of developing BPD in preterm infants, but questions about their safety remain. An alternative to inhalation is the intratracheal administration of corticosteroids using surfactant as a vehicle, but this approach has only been studied in a limited number of infants. We review the evidence for the short-term clinical efficacy and safety of inhaled, nebulized and intratracheal PCS for the prevention and treatment of BPD.

1. Introduction

The concern for adverse outcomes with the use of systemic postnatal corticosteroids (PCS) for bronchopulmonary dysplasia (BPD) [1], including gastrointestinal perforation in the short term, and cerebral palsy in the long term, likely led to the widespread use of alternatives to systemic PCS in routine clinical care [2-5]. The potential benefits of direct corticosteroid administration to the lungs include the need for lower medication doses compared with systemic administration, fewer systemic adverse effects, and a more rapid onset of action at the target organs [6, 7]. Corticosteroids can either be suspended in propellants and inhaled in metered doses, nebulized, or mixed with exogeneous surfactant and injected into the trachea. In analogy to systemic PCS, inhaled or intratracheal corticosteroids are believed to attenuate the inflammatory process associated with the development and the subsequent course of BPD [8].

The effect of inhaled corticosteroids for the prevention or treatment of BPD has been investigated in a number of randomized controlled trials (RCTs). However, the administration of inhaled corticosteroids is associated with a considerable uncertainty regarding drug delivery and deposition. To overcome the problem of poor delivery of the drug, direct instillation of corticosteroids into the lungs using surfactant as a vehicle has been proposed [9]. The mixing of surfactant with corticosteroids may ensure an adequate drug deposition and may result in a rapid and more uniform distribution of corticosteroids to the peripheral airspaces [10].

The purpose of this review is to discuss what is known about the short-term clinical efficacy and safety of inhaled, nebulized and intratracheal routes of PCS administration for the prevention and treatment of BPD.

2. Inhaled corticosteroids

2.1. Aerosol delivery systems

Various devices have been used for the delivery of aerosolized particles to the peripheral airways, including jet nebulization, metered dose inhalers, vibrating mesh, and ultrasonic. Jet nebulization and metered dose inhalers (MDIs) seem to be the two most common and effective options for newborns [11].

Jet nebulizers require a pressurized gas supply as the driving force for liquid atomization. This pressurized gas passes through a narrow orifice to form a jet, which sucks drug solution from a reservoir into a feed tube. The solution with the drug being drawn up from the fluid reservoir is then shattered into fine droplets. Baffles trap the larger droplets [12]. There are several advantages to jet nebulization, including that effective use requires only simple, tidal breathing and that intermittent or continuous drug administration is possible. Moreover, its design allows for dose modification and dose compounding. Disadvantages of jet nebulizers include the length of treatment time and the higher medication costs compared with metered dose inhalers. Moreover, a power source is required to generate the aerosol. At least two inhaled corticosteroids have been developed as nebulizer solutions; beclomethasone diproprionate, which is available in Europe and Asia, and budesonide [13].

MDIs are hand-held aerosol inhalers that use a propellant to deliver a therapeutic agent. MDIs include a canister containing the propellant and the formulation, a metering valve capable of delivering a consistent amount of drug with each dose delivered, and an actuator mouthpiece that atomizes the formulation and serves as a conduit to deliver the aerosol to the patient [14]. In newborns, coordinating the actuation with inhalation is challenging, therefore, ancillary devices such as spacers are used to limit medication loss in the oropharynx. The spacer can be

connected with a face mask in spontaneously breathing infants or attached to the inspiratory arm of the circuit or the endotracheal tube in mechanically ventilated infants. Because only intermittent drug administration is possible, treatment time is shorter with MDIs compared with a jet nebulizer.

2.2. Aerosol deposition in the newborn

There are a number of factors that limit penetration of aerosols into the lungs of newborns including the anatomy of the upper and lower airways, the physiologic and pathophysiologic condition of the patient, and the type and use of the aerosol delivery system (Table 1) [11].

Size distribution of particles has been shown to be the most important determinant of the quantity of inhaled particles that penetrate the tracheobronchial tree to reach the distal lung. The optimal aerosol particle size for the neonatal population is not known. However, as particle size decreases, the site of deposition within the respiratory tract becomes more peripheral [15]. A particle size <2 μm in diameter seems to be necessary to reach the very distal airways [16]. In newborns requiring respiratory support, the particles should be small enough to bypass that interface with minimal impaction losses, but should not be too small in order to avoid significant exhalation losses [17, 18].

To study the influence of various anatomical, physical, and physiological factors on aerosol delivery in preterm infants, a number of *in vitro* models of the upper and lower airways have been constructed. Minocchieri et al. developed an anatomically correct nose throat-model based on MRI data obtained from a premature neonate of 32 weeks gestational age [19]. Using a vibrating membrane nebulizer attached to the airway model with a facemask, the authors showed a reciprocal dependency between inspiratory flow and lung dose due to

higher inertial impaction of aerosol particles in the upper airways, resulting in decreasing aerosol penetration to the peripheral airways. Using a synchronized jet nebulizer and a neonatal test lung, Pelkonen et al. measured the dose of nebulized budesonide delivered through an endotracheal tube. The authors evaluated the effect of delivering the nebulized aerosol to two different locations in the same ventilatory circuit [20]; nebulizer output was highest when attached to the endotracheal tube directly. Other models tested aerosol delivery via MDIs and valved holding chambers during simulated spontaneous breathing and mechanical ventilation in neonates [21]. Aerosol delivery during mechanical ventilation via an endotracheal tube was less than during spontaneous breathing. Moreover, the amount of drug that was delivered was lowest if the spacer was left in line for five, compared with 15 and 30 breaths after MDI actuation [22]. Finally, another study compared aerosol delivery in a neonatal ventilated lung model using three delivery methods [23]: jet nebulizer, chlorofluorocarbon-pressurized MDI actuated into a spacer, and a hydrofluoroalkane-pressurized MDI actuated into a spacer. Administration via either device resulted in more efficient delivery than by nebulization.

While there are several studies measuring aerosol deposition in non-intubated infants and children [24-30], there is paucity of data regarding drug deposition in the neonatal population because of the inability to use radiolabeled aerosols. Fok et al. compared the radio-aerosol deposition of salbutamol by jet nebulizer and MDIs in mechanically ventilated and non-mechanically ventilated infants with BPD in a crossover design [17]. A larger dose of drug was delivered to the lungs by two puffs of inhalant from the MDI than from 5 min of jet nebulizer therapy. In both groups, as little as 1% of the initial dose actually reached the lungs, compared with 8-22% in adults [31].

2.3. Evidence for the efficacy of inhaled corticosteroids

At least three systematic reviews and meta-analyses are available comparing inhaled PCS with placebo or no intervention for infants with BPD. The two reviews in the Cochrane Library concentrated on early (treatment started before two weeks of age) and late (treatment started after seven days of age) use of inhaled corticosteroids, respectively [32, 33]. In contrast, a recent meta-analysis pooled all studies comparing inhaled PCS with placebo, whether they have been designed for the prevention, or the treatment, of BPD [34].

2.3.1. Early inhaled corticosteroids

Shah et al. included RCTs that administered inhaled PCS to very low birth weight infants beginning in the first two weeks after birth for the prevention of BPD at 36 weeks' postmenstrual age [32]. Early administration of inhaled PCS was effective in reducing the incidence of death or BPD at 36 weeks' postmenstrual age, and no significant effect on mortality by 36 weeks was noted (Table 2). The authors questioned the clinical relevance of their finding; the number needed to treat to prevent one infant from developing death or BPD at 36 weeks was 17 with the upper limit of the 95% confidence interval of infinity.

The largest individual trial in the review by Shah et al. is the Neonatal European Study of Inhaled Steroids (NEuroSIS) by Bassler et al., a placebo-controlled, double-blind RCT conducted in 40 centers in nine countries including 863 preterm infants with a gestational age of 23^{+0} to 27^{+6} weeks [35]. Infants were eligible if their chronological age was 12 hours or less, and they required any form of positive pressure respiratory support. The intervention group received inhaled budesonide at doses of 400 μg 12-hourly for 14 days, then 200 μg 12-hourly until either 32 weeks postmenstrual age, or until they had ceased respiratory support. The primary outcome, a composite of death or BPD at 36 weeks of postmenstrual age, was

40% (175/437) in the budesonide group compared with 46% (194/419) in the placebo group (RR 0.86; 95% CI 0.75, 1.00; *P* = 0.05). There was a substantial reduction in the rate of BPD, 28% (101/363) in the budesonide group versus 38% (138/363) in the placebo group (RR 0.74; 95% CI 0.60, 0.91; *P* = 0.004), however, death occurred in 17% (74/437) and 14% (57/419) of the patients, respectively (RR 1.24; 95% CI 0.91, 1.69; *P* = 0.17). The authors concluded that among extremely preterm infants, the reduction in the incidence of BPD with inhaled budesonide may have been gained at the expense of increased mortality.

The Cochrane reviews reported long-term outcomes following the use of inhaled PCS for two trials [36, 37]; There was no evidence for an effect of inhaled PCS on the rates of cerebral palsy, neurodevelopmental impairment or readmission to hospital due to respiratory infections. Not yet included in this Cochrane review, however, are the long-term outcomes of the NEuroSIS trial [38]. When this trial was planned, no effect of inhaled budesonide on mortality was suspected and thus, the prespecified long-term outcome did not include mortality as a component [35]. When the primary outcome was assessed it was noted that budesonide was associated with a nonsignificant increase in mortality [39]. Therefore, it was decided to assess additional exploratory long-term outcomes, including mortality at the time of the follow-up assessment and a composite outcome of death or severe neurodevelopmental disability. Neurodevelopmental disability among survivors was defined as a composite of cerebral palsy, cognitive delay (a Mental Development Index score of <85 [1 SD below the mean of 100] on the Bayley Scales of Infant Development version II), deafness, or blindness at a corrected age of 18 to 22 months. At the time of the follow-up examination, the prespecified long-term outcome, neurodevelopmental disability, was 48% in the budesonide and 51% in the placebo group (RR: 0.93; 95% CI: 0.80, 1.09; *P* = 0.40). There was no significant difference between the budesonide group and the placebo group with respect to the

composite outcome of death or neurodevelopmental disability (RR: 1.00; 95% CI: 0.89, 1.13, *P* = 0.97), but the results suggested higher mortality with budesonide (RR: 1.37; 95% CI: 1.01, 1.86, *P* = 0.04). Most deaths in the NEuroSIS trial occurred in the first week of life. Therefore, the difference in mortality observed at a corrected age of 18 to 22 months largely reflected the difference in mortality before hospital discharge. The authors speculated that the mortality difference may have arisen by chance, especially since no plausible explanation had been identified after a detailed review of the causes of death and clinical course of all study infants who died [40]. No adjustment was made in the analyses for multiple comparisons.

2.3.2. Later inhaled corticosteroids

Onland et al. included eight trials and 232 infants in their Cochrane review on later (commenced ≥7 days after birth) inhaled PCS [33]. The primary outcome, death or BPD at 36 weeks' postmenstrual age was reported by a single trial including 30 participants. Corticosteroid inhalation did not reduce the combined outcome of death or BPD nor its separate components (Table 2). Based on the limited data available, especially for important outcomes such as mortality and BPD, the authors recommended against the use of inhaled PCS initiated ≥7 days of life for preterm infants at high risk for developing BPD. None of the studies reported long-term neurodevelopmental sequelae.

2.3.3. Early and late inhaled corticosteroids

In contrast to the two Cochrane reviews on early and late inhaled PCS, Shinwell et al. reviewed the evidence for all studies comparing inhaled PCS with placebo for the prevention or treatment of BPD or death in preterm infants. Overall, sixteen RCTs met the criteria for inclusion with 804 infants in the active intervention groups, and 792 infants in the control groups. Again, more than half of the included infants were studied in the NEuroSIS trial [39].

In the inhaled PCS group, there was a beneficial effect on the incidence of BPD at 36 weeks with a number needed to treat of 14 infants (Table 2). There was no effect on mortality (Table 2). Another benefit of inhaled PCS found in this meta-analysis was a reduction in the use of systemic PCS as a rescue therapy (RR 0.87; 95% CI 0.76, 0.98, P = 0.03). The authors concluded that inhaled PCS may be considered for the prevention or treatment of BPD. Limited long-term outcome data of a single RCT including 60 participants were available for this meta-analysis and the conclusions of this meta-analysis need to be confronted with the long-term outcome data of the NEuroSIS trial.

2.4. Evidence for the safety of inhaled corticosteroids

A number of inhaled PCS have been tested in preterm infants including budesonide [39], beclomethasone diproprionate [41], fluticasone proprionate [42], and dexamethasone [43]. In clinical practice, beclomethasone and budesonide are used most frequently [2-4], even though data on their pharmacological and safety profile are limited [44]. Local adverse effects of inhaled PCS may include oral candidiasis and pneumonia. Pharyngeal candidiasis and laryngeal myopathy following corticosteroid inhalation may be rare in the neonatal population, since MDIs are frequently used with a spacer in this age group, likely resulting in less medication impaction in the oral pharynx and the larynx [45].

Systemic adverse effects may arise from corticosteroid absorption via the pulmonary vasculature circumventing the liver's first pass metabolism and via the gastrointestinal tract [46]. PCS have been shown to affect postnatal growth patterns of preterm born infants [47], however, studies on a potential suppression of the pituitary-adrenal axis provide conflicting results. Ng et al. evaluated the pituitary-adrenal function following inhalation with fluticasone in preterm infants [48]. A two-week course of inhaled fluticasone produced a moderately

severe suppression of adrenocorticotropic hormone and cortisol secretion in very low birth weight infants indicating a suppression of both the pituitary and adrenal glands. Similarly, a 28-day treatment period in very low birth weight infants for the prevention of BPD was associated with lower basal plasma cortisol levels [49]. However, the effect was small and its clinical significance unknown. Moreover, there was no suppression of adrenal secretory capacity after stimulation. Other adverse effects typically associated with systemic administration of PCS, such as hyperglycemia, hypertension, hypertrophic obstructive cardiomyopathy, and gastrointestinal hemorrhage and perforation, have not been increased in two recent meta-analyses on inhaled PCS for the prevention or treatment of BPD [32, 34].

The most worrisome effect associated with the use of inhaled corticosteroids arose with the publication of the primary outcome of the NEuroSIS trial [39]. The primary outcome (a composite of death or BPD at 36 weeks postmenstrual age) was of borderline significance favoring budesonide, due to the combination of a significant reduction in BPD, but a non-significant increase in mortality in the treatment group. Given the association between inhaled glucocorticoids and pneumonia in adults, it was postulated that a similar link might explain the potential increase in mortality [50]. However, a *post hoc* analysis of the NEuroSIS data did not confirm this association [51]. Reassuringly, appropriate meta-analyses did not show an effect of inhaled PCS on mortality [32, 34].

3. Intratracheal instillation of corticosteroids

Endotracheal administration of surfactant to reduce surface tension in the airways is standard practice in preterm infants with respiratory distress syndrome. Surfactant is a mixture of lipids and several specific surfactant proteins, which have a unique spreading property. Therefore, surfactant may be an efficient vehicle for pulmonary drug delivery, particularly for

corticosteroids [52]. Compared with inhaled PCS, it is expected that corticosteroids administered to the lung via the intratracheal route may have the potential to spread more evenly and reach the distal gas exchanging structures, thus, maximizing the anti-inflammatory effects in the distal airways [53]. In preterm infants, only two RCTs have been conducted to evaluate the effect of intratracheal instillation of PCS with surfactant [54, 55]. Both used budesonide together with surfactant. Budesonide has potent anti-inflammatory effects and undergoes extensive biotransformation in the liver with low systemic potency of its metabolites [56]. In the lung, budesonide is absorbed by lung cells and conjugated with fatty acids. This conjugation process is reversible, thus, there is a gradual release of free budesonide into the surrounding medium resulting in a prolongation of the local anti-inflammatory action [57].

3.1. **Pulmonary distribution of corticosteroids mixed with surfactant**

A number of animal models have investigated the distribution of PCS after tracheal instillation with surfactant. Nimmo et al. showed that radiolabeled dexamethasone administered into the trachea of rats with either surfactant or saline as a vehicle was well distributed throughout the lungs, including the periphery [58]. However, compared with saline, there was a significantly greater delivery of dexamethasone to the lobar midsections with surfactant. Furthermore, the surface properties of the surfactant-dexamethasone mixture were not altered. Huang et al. used an *in vivo* imaging system to analyze the effect of intratracheal surfactant and budesonide instillation on the pulmonary distribution of fluorescent dye in mice [59]. Almost no fluorescence was seen in the lung region of the control mice, however, the fluorescent intensity observed in the experimental groups increased by the following percentages: in the fluorescent dye group, 2%; in the fluorescent dye + surfactant group, 57%; in the fluorescent dye + budesonide group, 34%; and in the

fluorescent dye + surfactant + budesonide group, 100%. Therefore, the combined intratracheal administration of surfactant and budesonide enhanced the pulmonary distribution of fluorescent dye in mice compared with the administration of either surfactant or budesonide alone.

3.2. **Physical properties of corticosteroids mixed with surfactant**

All corticosteroids are biochemically derived from cholesterol [60]; hence, they share a close structural similarity. Cholesterol is the major neutral lipid in pulmonary surfactant with a concentration of up to 10% [61]. Depending on its concentration, cholesterol can significantly alter the molecular organization of surfactant films, thus varying their biophysical properties [62, 63]. Because of concerns that PCS delivered with surfactant may also compromise the surfactant's surface activity and thus worsen lung mechanics, studies on potential interactions between surfactant and the added PCS have been conducted. Yeh at al. demonstrated that 2% budesonide added to survanta (Abbott, Columbus, Ohio, USA) did not interfere with the surface activity of the suspension. In a concentration of 25%, however, budesonide blocked the ability of survanta to reduce the surface tension [54]. Palmer et al. found that the addition of budesonide at low (0.6%) and high (20%) concentration adversely affected the surface tension properties of two cholesterol-containing surfactant preparations (survanta, bovine lipid extract surfactant) [64], meanwhile Zhang et al. demonstrated that at low concentrations of 0.1% and 1%, budesonide had no deleterious effect on a cholesterol-free surfactant preparation (Curosurf, Chiesi Pharmaceuticals, Parma, Italy) [65]. Cimato et al. finally investigated whether beclomethasone, budesonide and fluticasone incorporated into surfactant (Prosurf, Nialtec S.A., Buenos Aires, Argentina) modified the surfactant structure and its activity [66]. Beclomethasone and budesonide caused a minimal increase in surface tension, although not enough to inactivate the surfactant. In conclusion, there is still disagreement

about potential adverse effects of these compounds on surfactant, depending on the type of exogeneous surfactant studied and on the amount of corticosteroid added.

3.3. Evidence for corticosteroids mixed with surfactant in neonates

There are only two RCTs that assessed intratracheal administration of PCS in preterm infants [54, 55]. Yeh et al. conducted a randomized pilot study in 116 very low birth weight infants (<1500 g) who had severe radiographic respiratory distress syndrome and required mechanical ventilation with fraction of inspired oxygen ≥0.60 shortly after birth. Infants were randomly allocated to budesonide 0.25 mg/kg mixed with 100 mg/kg surfactant (survanta) or to surfactant only. Doses of study medication were given every eight hours until the fraction of inspired oxygen was <0.30. The primary outcome of death or BPD at 36 weeks was less frequent in the budesonide group (31.7%; 19/60) than in the controls (60.7%; 34/56, P = 0.003). Other short-term benefits of intratracheal surfactant and budesonide included a better pulmonary status in terms of mean airway pressure and oxygenation index in the first days of life, lower rates of extubation failure, and shorter duration of fraction of inspired oxygen >0.40. No short-term adverse effects were noted during the study, or at the time of the follow-up assessment at 2-3 years of age [67].

Following the promising results of the pilot trial, Yeh et al. conducted a multicenter RCT with similar inclusion criteria and intervention and the same primary outcome, death or BPD [55]. 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 rate of BPD alone at 36 weeks was 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). Death alone at 36 weeks was not reduced: 13% (17/131) in the budesonide group vs 16% (22/134) in the controls (RR 0.96; 95% CI 0.87, 1.06; P = 0.54). Again, follow-up of infants showed no significant differences between the

two groups for growth and neurodevelopmental outcome, although not all children have yet been seen for follow-up.

Two meta-analyses synthesizing the evidence of budesonide mixed with surfactant for the prevention of BPD have been published [9, 68]. Both showed that the intratracheal instillation of surfactant with budesonide, compared with surfactant alone, reduced the odds of BPD at 36 weeks, death or BPD at 36 weeks, and significantly increased survival without BPD at 36 weeks.

4. Conclusions

There is increasing evidence from two meta-analyses that inhaled PCS may be associated with a significant reduction in BPD at 36 weeks. These meta-analyses are dominated by the NEuroSIS trial, in which there was the worrisome finding of a small but non-significant increase in mortality in the inhaled PCS group. No plausible explanation has been identified for the mortality finding in this study, and reassuringly, two meta-analyses did not find an effect of inhaled PCS on mortality.

Intratracheal instillation of PCS using surfactant as a vehicle soon after birth seems an effective strategy for the prevention of BPD, but this approach has only been studied in a very limited number of infants. Two large, multicenter RCTs (PLUSS trial - ACTRN12617000322336, Intratracheal Budesonide/Surfactant Prevents BPD trial - NCT03275415) will provide additional evidence on the effect and safety of this drug combination on preterm lung injury in the future.

Practice points

- The effective use of inhaled corticosteroids for preterm infants at risk of BPD is linked with a number of anatomical, physiologic, pathophysiologic and technical variables that impact aerosol delivery to the lungs.
- Current evidence suggests that inhaled corticosteroids may be an effective therapy in the management of developing BPD in preterm infants, but questions about their safety remain.
- At present, there is insufficient evidence to support the use of corticosteroids instilled into the trachea using surfactant as a vehicle.

Research directions

- More information on the efficacy and long-term safety of inhaled corticosteroids in selected high-risk infants is needed.
- Future research focusing on the design of aerosol delivery systems, the pharmacokinetics of inhaled corticosteroids, and the quantification of aerosol deposition in preterm infants with and without respiratory support is required.
- The safety of corticosteroids instilled into the trachea using surfactant as a vehicle needs to be established, particularly with regards to their long-term effects on the brain and lung.

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Conflict of interest

The authors declare no conflict of interest.

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Tables

Table 1. Factors limiting penetration and deposition of aerosols into the newborn lung

Anatomical	Physiologic	Pathophysiologic	Technical
Small oropharynx	Nasal breathing	Inflammation	Device: bigger particle size, large residual volume, non-synchronized actuation, placement of aerosol generator
Small airway diameter	Low tidal volume	Edema	Formulation: viscous, suspension
Airway obstruction	Low functional residual capacity	Atelectasis	Endotracheal ventilation: small endotracheal tube, humid gas, short inspiratory time
	High respiratory rate	Mucus	Spontaneous breathing: bad face mask position
	Shorter breath holding time	Bronchoconstriction	Operator: incorrect use

Table 2. Main outcomes from meta-analyses on inhaled corticosteroids for BPD

Outcome	No. of studies	Inhaled corticosteroids	Control	RR (95% CI)	P-value
Early inhaled corticosteroids [32]					
BPD at 36 weeks	6	24.1% (131/544)	31.4% (171/554)	0.76 (0.63, 0.93)	0.005
Death at 36 weeks	6	14.6% (95/649)	13.5% (86/636)	1.08 (0.83, 1.42)	0.57
Death or BPD at 36 weeks	6	34.9% (227/649)	40.3% (256/636)	0.86 (0.75, 0.99)	0.037
Later inhaled corticosteroids [33]					
BPD at 36 weeks	1	60.0% (9/15)	60.0% (9/15)	1.00 (0.59, 1.70)	1.00
Death at 36 weeks	3	0.07% (2/30)	0.00% (0/31)	3.00 (0.35, 25.78)	0.32
Death or BPD at 36 weeks	1	73.3% (11/15)	66.6% (10/15)	1.10 (0.74, 1.63)	0.65
Early and late inhaled corticosteroids [34]					
BPD at 36 weeks	7	25.6% (149/581)	32.7% (192/587)	0.77 (0.65, 0.91)	0.003
Death at 36 weeks	7	13.1% (84/639)	11.3% (71/631)	0.97 (0.42, 2.20)	0.93
Death or BPD at 36 weeks	6	34.9% (227/649)	40.3% (256/636)	0.86 (0.75, 0.99)	0.03

RR, risk ratio; CI, confidence interval; BPD, bronchopulmonary dysplasia