Seminars in Fetal and Neonatal Medicine 24 (2019) 202–206

Contents lists available at ScienceDirect

Seminars in Fetal and Neonatal Medicine

journal homepage: www.elsevier.com/locate/siny

Prophylactic postnatal corticosteroids: Early hydrocortisone

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ARTICLE INFO

Keywords:
Hydrocortisone
Bronchopulmonary dysplasia
Prematurity
Inflammation

ABSTRACT

Inflammation is a key contributor to the pathogenesis of bronchopulmonary dysplasia (BPD) in preterm infants, and cortisol plays a central role in controlling inflammation. Insufficient cortisol limits the ability of the sick newborn to handle stress and inhibit pulmonary inflammation. Evidence of lower cortisol and lower response to adrenocorticotropic hormone in infants subsequently developing BPD led to studies of early low-dose hydrocortisone to prevent BPD. Based on four randomised clinical trials enrolling almost 1000 extremely preterm infants, prophylaxis of early adrenal insufficiency with low-dose hydrocortisone significantly decreased BPD and mortality, as well as medical treatment for a patent ductus arteriosus. An increase in late-onset sepsis reported in the most immature infants had no adverse effect on mortality or neurodevelopmental outcomes. There was no increase in gastrointestinal perforation in the absence of indomethacin. The demonstrated beneficial effects of early low-dose hydrocortisone make a strong case for its use in extremely preterm infants at high risk for BPD.

1. Bronchopulmonary dysplasia: new features for an old disease

Advances in neonatal intensive care have led to substantial improvements in the survival rate of extremely preterm infants in the past decades. However, prevention and treatment of bronchopulmonary dysplasia (BPD), first described in 1967, remain elusive for this population [1]. BPD, one of the most significant morbidities of premature infants, refers to chronic lung injury after preterm birth [1]. The most common chronic lung disease of infancy, BPD is a major cause of mortality and poor neurodevelopmental outcomes [2,3]. While prematurity is the strongest risk factor for developing BPD, other hallmark risk factors in order of significance are gestational age, low birth weight, sepsis and patent ductus arteriosus (PDA) [4,5].

Classic BPD refers to the disease most common during the pre-surfactant era, characterized by focal inflammation, airway injury, fibrosis, parenchymal fibrosis secondary to ventilator-induced volutrauma and high supplemental oxygen concentration [1]. With the increase in survival of more immature infants, "*new BPD*" became more common, referring to a disease occurring after exposure to antenatal corticosteroids, exogenous surfactant and 'gentler' mechanical ventilation, characterized by an arrest of alveolar development, more diffuse inflammation, and less scarring and fibrosis. The new BPD has been conceptualized as a consequence of disrupted alveologenesis and angiogenesis [6]. Briefly, injuries attributed to mechanical ventilation have been diminished by newer ventilation methods, and inflammation remains the primary basis of the disease pathogenesis. While the natural history of the classic and new forms of BPD are not similar, both groups manifest respiratory symptoms and chronic functional respiratory abnormalities which follow into adolescence, and possibly into adulthood [7]. With the exception of caffeine [8], BPD has been generally resistant to postnatal therapies.

2. Adrenal function and relative adrenal insufficiency in the preterm newborn

Inflammation is a key contributor to the pathogenesis of BPD [9–12]. Cortisol plays a central role in controlling inflammation. This glucocorticoid hormone is produced by the zona fasciculata of the cortex of the adrenal glands and is responsible for an array of functions, including (but not limited to) metabolism and the immune system during physiological stress (physical, developmental, metabolic, immunologic, etc.) [13]. Fetal cortisol production is very limited before 23 weeks of gestation due to the immature hypothalamic-pituitary-adrenal axis (HPA); cortisol synthesis only reaches significant levels after 30 weeks of gestation [14–16]. Before that time, the fetus uses placental progesterone to synthesize cortisol. Therefore, earlier delivery hinders the ability of the extremely preterm newborn to maintain homeostasis during the intense stressors of extrauterine life in the newborn intensive care unit, which include supplemental oxygen exposure, infection, mechanical ventilation, painful and stressful procedures, and noxious

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https://doi.org/10.1016/j.siny.2019.04.007

sensorineural stimuli. The lack of adequate serum cortisol as one of the main contributing factors to the inflammatory-driven BPD development is a well-accepted theory, as insufficient cortisol limits the ability of the neonate to handle stress and adequately regulate the immune system by inhibiting unnecessary pulmonary inflammation [1].

The fact that cortisol is central to an individual's ability to respond to inflammation led to investigation of adrenal function in the preterm infant. Beginning with small studies in the early 1990s, investigators have reported surprisingly low cortisol concentrations in sick very preterm infants [17–19]. In 1995, two publications described lower cortisol concentrations in the first postnatal week in very low birth weight babies (< 1500 g birth weight) who were receiving vasopressor support, as well as lower cortisol values and lower response to adrenocorticotropic hormone (ACTH) in infants who subsequently developed BPD [17,20]. The combination of increased inflammation and low cortisol concentrations seen in these infants led to the hypothesis that extremely preterm infants are at risk for a relative adrenal insufficiency (RAI) due to developmental immaturity.

RAI is defined as an inability to produce sufficient cortisol to respond to significant stressors, such as critical illness, and a central feature of RAI is cardiovascular insufficiency, with hypotension responsive to glucocorticoid treatment [21]. The presence of RAI in extremely preterm infants would be a logical result of limited enzymatic capacity to produce cortisol in the extremely preterm newborn. For example, one of the critical enzymes in the cortisol pathway, 3-beta hydroxysteroid dehydrogenase, is not expressed in the normally progressing pregnancy until about 23 weeks of gestation [13]. In a clinically relevant animal model, the preterm baboon, a significant percentage of extremely preterm newborns have decreased cortisol production early in life with associated cardiovascular dysfunction, reversible with hydrocortisone [22].

In the human newborn, investigators have documented for many years that sicker preterm infants generally do not have higher cortisol concentrations than well infants, and can have lower response to stimulation of the HPA axis [18,19,23–25]. At the same time, most have reported that these infants have higher concentrations of cortisol precursors, suggesting that the HPA axis is being stimulated but lacks the enzyme capacity to respond well [18,25,26]. Several additional findings over the years have supported the hypothesis that extremely preterm infants can have RAI, including lower cortisol values in infants with patent ductus arteriosus, an inverse relationship between markers of inflammation in the lung and cortisol values, and lower concentrations in hypotensive infants [17,24,27].

The appropriate therapy for a patient with RAI is not high-dose glucocorticoid treatment, but replacement of physiologic cortisol concentrations. Thus, with evidence of lower cortisol and lower response to ACTH in infants subsequently developing BPD, as well as in those receiving vasopressor support for cardiovascular insufficiency, studies of hydrocortisone to prevent BPD were undertaken.

3. Steroids to improve outcomes following very preterm delivery: towards a more physiologic and prophylactic strategy

Given the nature of the disease process, with fixed variables such as prematurity and immature lungs, preventive methods have mainly focused on modifiable factors, such as ventilation and oxygenation strategies, and glucocorticoid supplementation. Extensive advances have been made with ventilation and oxygenation therapy, leading to more appropriate, shorter invasive respiratory support [28]. Non-steroidal anti-inflammatory drugs have been shown to be ineffective in ameliorating BPD, likely because their mechanism of action is limited to inhibiting only a few pathways of the inflammatory cascade, mainly the cyclooxygenase pathway [29]. Glucocorticoids are much more potent anti-inflammatory molecules, dampening the entirety of the immune response by interacting with nuclear genes, inhibiting inflammatory precursor molecules such as arachidonic acid, and impacting immune cells directly [30].

Systemic (intravenous or enteral) postnatal corticosteroids (PCS) have been used for decades to decrease the incidence and/or severity of BPD [31,32]. Dexamethasone was used in the first published studies because of two properties which would later prove to be significant drawbacks to its use: “because of its nearly complete glucocorticoid activity and its long half-life.” [33]. Although these authors cautioned that “treatment cannot be recommended without further study of patient selection, dosage schedules, short and long-term side selection, dosage schedules, short and long-term side effects, and the mechanisms of its action,” the short-term benefits led to wide adoption of the therapy. Dexamethasone's lack of mineralocorticoid activity, together with its effect of suppressing endogenous cortisol production, led to an imbalance between binding of the mineralocorticoid receptors in the brain, occupied by cortisol under basal concentrations, and the glucocorticoid receptors, usually occupied by cortisol only under stressful conditions. By binding only to glucocorticoid receptors, dexamethasone led to apoptosis in areas of the brain critical to learning and memory, such as the hippocampus [34]. In addition, its long half-life amplified both its potency and its suppression of the HPA axis [35]. These features are likely central to the adverse effects seen with the use of dexamethasone in the extremely preterm infant. Thus, although dexamethasone clearly decreases BPD, many concerns regarding both short- and long-term adverse effects have surfaced, leading to a decrease in use and a consequential increase in BPD incidence in the recent decade [36]. Immediate side effects included hyperglycemia, hypertension, hematemesis, cardiac hypertrophy and gastrointestinal perforation; however, the most serious side effect observed following systemic dexamethasone use is an increase in the incidence of cerebral white matter damage and clinically apparent growth restriction and neurologic impairment [37–40]. This effect on brain growth and injury is more common when gestational age at birth is lower and when PCS are administered in the first postnatal week. Volumetric magnetic resonance imaging performed at term-equivalent age showed that dexamethasone induced a decrease in brain growth affecting both the cortex and basal ganglia, and decreased brain surface and gyration index [41]. In 2017, a Cochrane review concluded there was not enough evidence to establish a dose or regimen with dexamethasone or another corticosteroid to yield a positive benefit-to-risk ratio [42]. Nonetheless, systemic dexamethasone remains widely used. An extensive observational study conducted in Europe at all major teaching hospitals found that 67% of centres used systemic PCS. Of those, 48% initiated treatment on non-intubated infants, and 53% began therapy at 7–14 days of life [31]. In the US, one report from a very large administrative database showed that dexamethasone exposure for the most immature infants (less than 26 weeks' gestation) remained at 30–40% [36].

Factors to consider in determining the best PCS strategy for preterm infants include the type, dose, regimen, administration route, and duration of the treatment. Intravenous and inhaled routes of delivery have been primarily studied. A retrospective cohort study evaluating 1429 infants with BPD concluded that inhaled steroids were used on 25% of the population [32]. However, numerous studies have demonstrated significant variability of the effect of inhaled steroids, attributed to the method of delivery, low bioavailability, and practical issues in ventilated patients. Therefore, systemic administration currently appears to be the most practical alternative. Regarding the dose, the regimen and duration of treatment, several studies, including a 2014 Cochrane review, concluded that, with all PCS, a low dose with a short overall duration of treatment is the best strategy to yield a positive benefit-to-risk ratio [43]. If RAI contributes to the pathogenesis of BPD, it seems that the best approach would be using hydrocortisone, identical to native cortisol, in a dose high enough to act as a “physiologic replacement”, but low enough to avoid excessive immunosuppression. This hypothesis led to testing “low-dose” hydrocortisone as the most appropriate alternative to dexamethasone in preterm infants born

before 28 weeks of gestation.

4. Effects of early hydrocortisone replacement in very preterm infants

Among 11 randomised controlled trials testing HC early after birth reported to date, five have been specifically designed to test the efficacy of prophylaxis of early adrenal insufficiency to improve survival without BPD and other neonatal outcomes following very preterm delivery [44–48]. Other trials included more mature newborns, treated for different indications, such as refractory hemodynamic failure, or treated in combination with other drugs, including inotropes or thyroid hormones [49–54]. Watterberg et al. first described a randomised, double-blinded placebo-controlled pilot study conducted to compare treatment with low-dose hydrocortisone started before 48 postnatal hours to placebo. Based on pilot data, a dose of 0.5 mg/kg/q 12 h was given for 9 days, followed by 0.5 mg/kg/d for three days [44,55]. Forty mechanically ventilated infants weighing less than 1000 g were enrolled. In this pilot study, early treatment with low-dose hydrocortisone significantly increased the likelihood of survival without BPD, particularly in infants born after exposure to chorioamnionitis.

Five years later a larger multi-centre randomised controlled trial (RCT) enrolled 360 mechanically ventilated infants with birth weight of 500 g–999 g to receive hydrocortisone 0.5 mg/kg/q 12 h for 12 days, then 0.5 mg/kg/d for three days, or saline placebo, initiated between 12 and 48 h of life [45]. Cortisol concentrations obtained at the end of the first week showed that this HC dose resulted in a median increase of 5 mcg/dl. The trial was stopped because of an increase in spontaneous gastrointestinal perforation in the hydrocortisone group, attributed to the combination of indomethacin for PDA treatment and hydrocortisone. Hydrocortisone did not improve survival without BPD in the overall study population; however, treatment of chorioamnionitis-exposed infants significantly decreased mortality and improved survival without BPD.

Two other small RCTs showed promising results but were stopped before completion. Peltoniemi et al. enrolled a total of 51 infants with birth weight less than 1251 g or born at less than 31 weeks' gestation, who were under 36 h old and receiving mechanical ventilation in three NICUs in Finland [46]. Infants were stratified by centre and by birth weight, and were randomly allocated to a 10-day tapering course of hydrocortisone (2 mg/kg/d for two days, 1.5 mg/kg/d for two days, 0.75 mg/kg/d for six days) or saline placebo. This study was stopped because two of the hydrocortisone-treated infants had intestinal perforation, and other RCTs of early hydrocortisone had reported the same complication. Whilst the incidence of BPD was lower in the hydrocortisone group (28% vs placebo 42%, P = 0.28), this was not statistically significant; the incidence of PDA was significantly lower with hydrocortisone treatment (36% vs 73%, P = 0.01). Bonsante et al. enrolled a total of 50 infants of birth weight less than 1250 g or born at 24–30 weeks' gestation, who were less than 48 h old and were receiving mechanical ventilation after surfactant treatment [47]. Infants were randomly allocated to a 12-day course of hydrocortisone (1.0 mg/kg for nine days, then 0.5 mg/kg/d for three days) or saline placebo. The study was stopped early when 50 infants had been enrolled because of reports from other trials of spontaneous intestinal perforation with early hydrocortisone treatment. This trial suggested that hydrocortisone could improve oxygen-free survival at 36 weeks postmenstrual age and early cardiovascular function in very preterm infants.

In 2010, Doyle et al. concluded that there was a need for a larger RCT to finally confirm the true effect of hydrocortisone on BPD [56]; later, in a 2014 Cochrane review, Doyle et al. concluded that most beneficial and harmful effects were seen with dexamethasone, and that hydrocortisone had little effect on outcomes [43]. Together, these reviews confirmed a need for a large scale RCT with hydrocortisone.

Baud et al. conducted a multi-centre double-blind RCT of 523 infants born at 24–27 weeks' gestational age who were recruited from 21 French tertiary care perinatal centres in the first 24 h [48]. Enrolled infants received either hydrocortisone 1 mg/kg/d divided into two doses for seven days, then 0.5 mg/kg/d once per day for three days (cumulative dose, 8.5 mg/kg), or 5% glucose placebo. In this study, the rate of survival without BPD at 36 weeks of postmenstrual age (PMA) was significantly increased in the hydrocortisone group: (60% vs 51% in the placebo group (odds ratio [OR] adjusted for gestational age group and interim analyses 1·48, 95% CI 1·02–2·16, p = 0·04)). A positive safety and efficacy profile for hydrocortisone was demonstrated, despite a significant increase in late-onset sepsis, as there were no negative effects on neonatal mortality and neurodevelopmental outcomes. Subjects were prospectively followed for an additional two-year period to assess neurological outcomes, showing that hydrocortisone was not associated with any neurodevelopmental issues at two years of age [57]. These results are consistent with those of Watterberg et al., who reported that hydrocortisone-treated infants in that trial had no increase in neurodevelopmental impairment at two years, with some evidence of improved outcomes, including a decrease in the incidence of a Mental Development Index less than 70 on the Bayley Scales of Infant Development II (BSID-II), and an increase in awareness of object permanence [58]. Furthermore, in an exploratory analysis of neurodevelopmental outcomes in the Baud et al. trial, hydrocortisone was associated with a statistically significant improvement in neurodevelopmental outcomes in infants born at 24 and 25 weeks of gestation [59]. Notably, the hydrocortisone-treated infants had a lower incidence of moderate-to-severe neurodevelopmental impairment (2% vs 18% in the placebo group (risk difference −16% (95% CI −28% to −5%)). Consistently, the direction of the mean developmental quotient scores, although not significantly different between treatment groups, favoured hydrocortisone.

An individual patient data meta-analysis of these early hydrocortisone trials published in 2018 confirmed a significant benefit in survival without BPD and in survival to discharge [60].

5. Other systemic effects of early hydrocortisone in very preterm infants

Low cortisol concentrations have been associated with severe illness in preterm infants [17,19,23,24]. In addition to BPD, lower cortisol levels during the first week of life were associated with increased inflammatory markers in the lungs and a higher rates of PDA, another risk factor for BPD [20]. Not surprisingly, hydrocortisone has been reported to improve function in several other systems in addition to the developing lungs, including hemodynamics, electrolyte homeostasis, PDA closure and renal function [61]. The mineralocorticoid properties of hydrocortisone could play a role in these secondary beneficial effects.

The two side effects reported when using early hydrocortisone in extremely preterm infants were gastrointestinal perforation and late-onset sepsis [60]. However, the increased risk of spontaneous gastrointestinal perforation was observed only when hydrocortisone was given concurrently with indomethacin [45]. In addition, although the risk of late-onset sepsis was increased in infants exposed to hydrocortisone, no adverse effects were reported on either death or two-year neurodevelopmental outcomes [59].

6. Conclusion

While systemic hydrocortisone therapy is becoming more common in immature newborn infants with hemodynamic failure, adding this drug as first line treatment for either hemodynamic failure or prevention of BPD remains controversial. An individual patient data meta-analysis of RCTs including almost 1000 extremely preterm infants showed that prophylaxis of early adrenal insufficiency using low-dose hydrocortisone resulted in improved survival without BPD and a decrease in pharmacologic treatment for PDA, without adverse effects on

neurodevelopment at two years of age. When assessing risks, gastrointestinal perforation appears to be avoidable by using ibuprofen rather than indomethacin to treat PDAs, and the increase in late-onset sepsis had no detectable adverse effect on neonatal mortality or neurodevelopmental outcomes. In addition, the most immature infants have the highest rate of BPD and other prematurity-related complications. Given the demonstrated beneficial effects of hydrocortisone in extremely preterm infants at high risk for BPD, a strong case can be made for using early, low-dose systemic hydrocortisone in these infants.

Practice points

- Insufficient cortisol reduces the ability of very immature infants to face perinatal stress and inflammation.
- Early low-dose hydrocortisone improves survival without bronchopulmonary dysplasia in extremely preterm infants
- An increased rate of patent ductus arteriosus closure has been reported in infants treated with early low-dose hydrocortisone
- No adverse neurodevelopmental outcome has been observed following early low-dose hydrocortisone

Research directions

- The causal relationship between hydrocortisone exposure and patent ductus arteriosus closure
- How to better select subgroups of patients highly responsive to hydrocortisone
- The role of hydrocortisone in the risk of secondary sepsis in very immature infants

Conflict of interest

None of the authors have a conflict of interest.

Acknowledgements

This work was supported by a research grant from the French Ministry of Health and sponsored by the Département de la Recherche Clinique et du Développement, Assistance Publique-Hôpitaux de Paris (AOM 06 025 and AOM 11 129).

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