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The use of inhaled corticosteroids in chronically ventilated preterm infants

Leif D. Nelin*, J. Wells Logan

Comprehensive Center for Bronchopulmonary Dysplasia, Nationwide Children's Hospital, Columbus, OH, USA

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A B S T R A C T

Bronchopulmonary dysplasia (BPD) is the most usual reason for preterm infants to require chronic mechanical ventilation. Inflammation is a key factor underlying the lung injury leading to the development of BPD, and the rationale for use of corticosteroids in the management of ventilator-dependent preterm infants is based on their anti-inflammatory effects. Because systemic corticosteroids are associated with significant adverse effects in preterm infants, attention has turned to the use of inhaled corticosteroids (ICS) as a potentially safer therapy for BPD. The aim of this review is to discuss what is known about the efficacy and safety of ICS in chronically ventilated preterm infants. However, this has been a challenge since there is a paucity of high-grade evidence for the use of ICS in these patients. Thus, there is a real need for well-powered randomized controlled trials examining short- and long-term outcomes of ICS use in this population.

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1. Introduction

Bronchopulmonary dysplasia (BPD) is the morbidity most frequently associated with preterm birth in the USA, and the vast majority of preterm infants requiring chronic mechanical ventilation have BPD [1]. Advances in neonatal intensive care have led to greater rates of survival in preterm infants, but there has been no decrease in the incidence of BPD in survivors [2]. Infants with BPD are more likely to be readmitted to the hospital and more likely to die than preterm infants without BPD [1]. Moreover, survivors have higher rates of respiratory dysfunction [3] and neurodevelopmental impairment [4] than do those without BPD.

The current definitions of BPD are based on the need for supplemental oxygen at 28 days and/or 36 weeks postmenstrual age (PMA). The National Institutes of Health Office of Rare Diseases Research consensus definition of BPD, which was developed in 2001 and is the definition most widely used in the neonatal literature, is a requirement for supplemental oxygen for at least 28 days in infants born at <32 weeks PMA, and further classifies BPD as mild, moderate, or severe, based on the supplemental oxygen need and the need for positive pressure at 36 weeks PMA [5]. Due to issues with classification, various definitions have been proposed for BPD over the years [6]. Existing definitions differ with respect to ease of data collection and the number of unclassifiable cases [7]. Further, recent changes in management, such as the use of high-flow nasal cannula, have limited the application of existing definitions. A recent retrospective cohort study from the Canadian Neonatal network examined the reliability of using various definitions of BPD to predict outcomes [8]. Defining BPD using oxygen requirement alone, at various postmenstrual ages, was less predictive than using oxygen/respiratory support as criteria. The authors concluded that oxygen/respiratory support is a better indicator of chronic respiratory insufficiency than use of oxygen at 28 days or 36 weeks [8]. Clearly a contemporary definition of BPD is needed that correlates respiratory morbidity with disease pathophysiology, while at the same time improving the ability to classify BPD.

Despite issues with definitions, it is clear that inflammation is a key factor in the development and pathophysiology of BPD, and therefore a major determinant of the need for chronic mechanical ventilation in preterm infants. Thus, attention has turned to using corticosteroids as a potential therapy for the prevention and management of BPD. Systemically administered corticosteroids have been widely used in the treatment of preterm infants at risk for developing BPD and in infants with established BPD. However, the use of systemic corticosteroids has been found to increase the risk of death or cerebral palsy in preterm infants [9]. Clinicians have therefore turned to inhaled corticosteroids (ICS) as a potential

* Corresponding author. 575 Children's Crossroads, Columbus, OH 43215, USA.
E-mail address: Leif.Nelin@nationwidechildrens.org (L.D. Nelin).

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means of gaining the beneficial effects of corticosteroids, while minimizing the adverse effects of corticosteroids given systemically [10,11].

The aim of this chapter is to discuss what is known about the efficacy of ICS in chronically ventilated preterm infants, the vast majority of whom have BPD. Pursuing this aim, however, has posed a challenge since there is a paucity of evidence for the use of ICS in chronically ventilated preterm infants. Furthermore, many of the available clinical studies have examined the efficacy of ICS given early in the course of a preterm infant's neonatal intensive care unit (NICU) stay for preventing the development of BPD. Very few studies have examined the efficacy of ICS in chronically ventilated preterm infants.

2. Physiological rationale for ICS usage in BPD

Bronchopulmonary dysplasia has a complex pathophysiology, which often depends on when the underlying prenatal insults occurred and/or when birth occurred [12]. Whether it is the gestational age at the time of the prenatal insult or the gestational age at birth, anything that interrupts or interferes with lung development increases the risk of developing BPD. Moreover, a variety of genetic, endogenous, and exogenous factors may influence the natural history of BPD, and these factors may occur prenatally, during labor and delivery, or during the NICU stay (Box 1). For example, antenatal steroids confer a significant benefit [13], whereas necrotizing enterocolitis and sepsis confer an increased risk [4], as do hyperoxia, hypoxia, and poor nutrition [14,15]. The net sum of these exposures, favorable and unfavorable, ultimately determines the pulmonary outcome [15]. Inflammation occurring at any of these times has been associated with the development of, or worsening of, BPD. For example, blood cytokine profiles are increased in most inflammatory conditions, and preterm infants who go on to develop moderate/severe BPD have been found to have augmented blood cytokine concentrations [16]. Similarly, preterm infants with biomarkers of inflammation were shown to be at greater risk of developing BPD than those without such biomarkers [17]. Inflammatory stimulation of the immune system leads to the release of reactive oxygen species, chemokines, and cytokines from leukocytes that then may lead to pulmonary infiltration of activated neutrophils and macrophages leading to a cascade of lung injury that may result in the development of BPD. This has led to the use of corticosteroids in the treatment of established BPD for their anti-inflammatory effects [12].

Box 1
Factors that may influence the development of bronchopulmonary dysplasia.

Prenatal
Genetic predisposition
Exogenous exposures (i.e. antenatal steroids)
Chorioamnionitis
Intrauterine growth restriction
Gender, race
Labor and delivery
Gestational age at birth
Birth weight
Birth hospital
Quality of neonatal resuscitation
Postnatal
Invasive mechanical ventilation
Cumulative oxygen exposure
Patent ductus arteriosus management
Infection and/or inflammation
Nutrition
Postnatal systemic steroid use

Systemically administered corticosteroids remain the surest way of delivering steroids, especially to extremely preterm babies [9]. In preterm infants, systemic corticosteroids have been shown to reduce lung inflammation, leading to improvements in pulmonary function that facilitate weaning from mechanical ventilation [18]. Unfortunately, the use of systemic steroids in preterm infants is associated with significant adverse side-effects, including metabolic derangements, poor somatic growth, and neurodevelopmental impairments [4,19]. Studies have identified inflammatory biomarkers in both tracheal aspirates and lung lavage fluid from patients who go on to develop BPD [20]. Chemokine concentrations are increased in RDS and the concentrations have been correlated with the development of BPD. For example, recruitment to the lungs and the activation of neutrophils and macrophages in the lung are mediated by chemokines, which are increased in tracheal aspirates among infants that are oxygen dependent at 28 days and 36 weeks gestational age [21]. Generally speaking, preterm infants with biomarkers of inflammation are at greater risk of developing BPD than those without such biomarkers [17]. Gupta and colleagues found that early ICS significantly reduced biomarkers of pulmonary inflammation [interleukin (IL)-8 and IL-1ra concentrations] after only one week of treatment [22]. These findings support a potential role of ICS in mitigating the inflammation associated with the development of, and the subsequent course of, BPD.

The use of ICS has been shown to control airway hyperresponsiveness in childhood asthma. A large subset of preterm infants with BPD have lower airway flow rates, expiratory lung volumes, diffusion capacities, and more airway obstruction than do term infants without BPD [23,24]. These alterations in pulmonary function may be long-lasting, and it has been reported that school-age children with a history of BPD had clinically significant reductions in airflow (FEV1, FEV25-75, FVC) [3,25]. The physiologic rationale, then, for use of ICS in the management of ventilator-dependent infants with evolving BPD is that ICS decrease the inflammation and airway hyper-responsiveness, presumably mediated by inflammation, which so frequently accompanies BPD.

3. Studies examining the use of ICS for the prevention of BPD

Our review of the literature identified only seven reports [26–32] that examined the use of ICS in intubated preterm infants to prevent the development of BPD (Table 1). The ICS studies included fluticasone, beclomethasone, and budesonide. The largest study published to date examined the early use of budesonide in 863 infants born at 23–27 weeks gestation requiring intermittent positive pressure ventilation for the first 12 h of life, and examined the rates of the combined outcome of BPD or death, where BPD was defined as an oxygen requirement at 36 weeks PMA [32]. The authors found that early budesonide treatment did not significantly decrease the combined outcome of death or BPD [relative risk (RR): 0.86; 95% confidence interval (CI): 0.75–1.00; $P = 0.05$], but that early budesonide decreased the incidence of BPD (RR: 0.74; 95% CI: 0.60–0.91; $P = 0.004$), suggesting that the decrease in BPD may have been at the expense of increased mortality [32]. Of the remaining six studies, five examined BPD rates [26,27,29–31], and all five studies found no effect of early ICS on the rate of BPD in treated infants. The study by Fok et al. demonstrated improvements in respiratory system compliance in treated infants [26]. A few of the studies demonstrated a decrease in the number of days on mechanical ventilation in the patients receiving ICS compared to

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