Prevention of Bronchopulmonary Dysplasia: Are Intratracheal Steroids with Surfactant a Magic Bullet?

Bronchopulmonary dysplasia (BPD) remains the most common pulmonary cause of mortality and long-term morbidity in preterm infants. The two major pharmacologic advances in perinatal medicine have been antenatal corticosteroids to decrease the incidence of respiratory distress syndrome (RDS) (1) and surfactant to treat RDS (2). However, both therapies increase the survival of the most fragile extremely low-birth weight infants, and thus increase BPD in survivors (3).

Postnatal corticosteroids have been extensively trialed to improve lung function in preterm infants. Systemic steroids have been given soon after birth to prevent lung injury (4) and are commonly used later in the clinical course to blunt the progression to BPD, but with serious concerns about significant adverse effects (5). However, steroids do suppress the inflammation associated with injury of the preterm lung from supplemental oxygen and mechanical ventilation.

Aerosolized steroids seem to be minimally effective for the prevention or treatment of BPD in preterm infants, likely related to their inefficient delivery (6, 7). The search for a safe and effective way to use steroids to improve outcomes for preterm infants at risk of BPD without harm has continued for more than 30 years.

In this issue of the Journal, Yeh and colleagues (pp. 86–95) report a clinical trial comparing an initial surfactant treatment that includes budesonide with surfactant alone for preterm infants with severe RDS to decrease BPD (8). The surfactant/budesonide mixture decreased BPD by 21% (P < 0.001) with no acute adverse effects and no effect on neurodevelopmental outcomes at 2–3 years. After the first dose, the surfactant/budesonide or surfactant treatments were repeated if infants met criteria for repeat surfactant doses, with most of the study infants receiving only one or two doses of intratracheal budesonide and surfactant.

Budesonide with surfactant decreased oxygen requirements and improved oxygenation index during the first weeks of life. This combined therapy also reduced the severity of lung injury, as reflected by less moderate to severe BPD with no difference in mild BPD. Consistent with an anti-inflammatory effect of budesonide, cytokines in tracheo-alveolar fluid decreased in the budesonide-exposed infants relative to surfactant-treated infants.

The advantages of using budesonide locally are an onset of action early in the clinical progression to BPD, prolonged local anti-inflammatory effects, and decreased risk of systemic adverse effects. Of note, early inhaled budesonide was studied in premature infants and modestly decreased death or BPD (9). The lack of more striking effects of inhaled budesonide may have resulted from a less efficient delivery, or perhaps the patient populations studied. The use of surfactant as a vehicle to distribute drugs has been explored for years in animal models, and it works. As both surfactant and budesonide are available, the treatment can be given “off-label” without regulation, which has its benefits and risks. If the striking pulmonary benefits with absent detrimental effects described by Yeh and colleagues are replicated in large randomized controlled trials done in different clinical settings, this could very well become a “magic bullet” in the prevention of BPD.

It is important to point out that the current study enrolled only very-low-birth-weight infants with severe RDS, with almost one-third of infants with birth weights higher than 1,000 g. This resulted in a broad patient population, which although clinically similar in the two groups, was at different stages of lung development and may have had different lung pathologies. It would be important to know whether budesonide has similar positive effects in the infants of lower gestational age and earlier stages of lung development who are at the highest risk for severe BPD.

Despite the proven benefit of systemic postnatal steroids to reduce BPD, their use has significantly declined over the years because of the risk for adverse neurodevelopmental outcomes. Although the study was not powered to test effects on neurodevelopment, it is most reassuring that there was no increase in adverse neurodevelopmental outcomes at 2–3 years of age. Local administration of budesonide likely did not cause high systemic steroid levels (10). Future studies need to evaluate this intervention in infants of different gestational ages and with different severity of RDS and risks of neurodevelopmental impairment to better define the patient population for maximum pulmonary benefit.

This study included infants with severe RDS who will have a higher incidence of BPD. However, at the present time, the majority of infants who develop BPD are extremely premature infants who initially may have only mild RDS and not receive surfactant treatment (11). It is important to know whether treating this population with milder initial disease would have similar beneficial effects. Although initiating anti-inflammatory therapy early may have advantages for avoiding early damage, a larger population of high-risk VLBW infants would be exposed, many without benefit if they otherwise would not develop BPD. This population of VLBW infants is frequently exposed to antenatal infection, which is associated with an increased risk for BPD. It would be important to know whether infants born of mothers with chorioamnionitis will benefit from this therapy.

In summary, intratracheal administration of budesonide with surfactant soon after birth is a simple intervention that provides a unique opportunity to use an effective therapy for prevention of BPD specifically targeting the lung and to minimize the risks of systemic adverse effects. As both surfactant and budesonide are available, the treatment can be given “off-label” without regulation, which has its benefits and risks. If the striking pulmonary benefits with absent detrimental effects described by Yeh and colleagues are replicated in large randomized controlled trials done in different clinical settings, this could very well become a “magic bullet” in the prevention of BPD.

Author disclosures are available with the text of this article at www.atsjournals.org.

Eduardo Bancalari, M.D.
Deepak Jain, M.D.
Division of Neonatology
University of Miami Miller School of Medicine
Miami, Florida
References


Copyright © 2016 by the American Thoracic Society