Rescue therapy with betamethasone in preterm infants (day of life > 14) at high risk for bronchopulmonary dysplasia to assist weaning from ventilator support: a case series

Abstract

Background: Prolonged mechanical ventilation significantly increases the risk of bronchopulmonary dysplasia (BPD), a type of chronic lung disease (CLD) associated with significant morbidity and mortality in preterm infants. Postnatal steroid use is controversial, but a short course of intermittent, low-dose betamethasone might assist weaning from ventilator support and prevent some of the side effects from prolonged use of steroids.

Purpose: To evaluate the effectiveness of postnatal betamethasone in assisting with weaning from ventilator support.

Methods: A retrospective descriptive design was used for preterm infants who were treated with a short course of low-dose (defined as 2 or 3 doses of 0.10 to 0.15 mg/kg administered over 48 to 72 hours), intramuscular betamethasone (after two weeks of life) between November 1, 2017 and April 30, 2018. The electronic medical records of study infants were reviewed to establish the timeframe of successful ventilator weaning.

Results: Four infants with multiple risk factors for the development of BPD were successfully weaned from ventilator support within 48 hours of receiving a course of betamethasone therapy. Clinical and radiologic data were consistent with oxygen dependence and the need for ventilator support by day of life (DOL) 14. A two to three-day course of betamethasone was administered and the infants were weaned from ventilator support on subsequent days.

Implications for Practice: These data support the use of postnatal betamethasone as an alternative to dexamethasone for assisting weaning from ventilator support in preterm infants at high risk for developing BPD. The use of postnatal betamethasone may contribute to a decreased incidence of BPD and associated morbidity and mortality in this high-risk population.

Implications for Research: This is the first reported case series using rescue betamethasone therapy for assisting with ventilator weaning in infants born prematurely. Before generalizations can be made as to the safety and efficacy of this postnatal betamethasone regimen as compared to alternative steroid regimens in this high-risk population, large multicenter randomized controlled trials are required.

Keywords: neonatal, prematurity, bronchopulmonary dysplasia, chronic lung disease, corticosteroid, ventilation

Background

Bronchopulmonary dysplasia (BPD) is a form of chronic lung disease (CLD) that is a major sequel of respiratory distress syndrome (RDS) associated with significant neonatal mortality and long-term morbidity in survivors. The incidence is highest in babies born at less than 28 weeks of gestation who have severe respiratory distress at birth, particularly in those who require respiratory support with oxygen and positive-pressure ventilation for more than two weeks after birth. Despite the high prevalence of BPD among the increasingly immature population of infants surviving preterm birth, no drugs for prevention have been licensed. Persistent lung inflammation is the most likely mediator of lung injury contributing to the development of BPD.

The role of corticosteroids as anti-inflammatory agents has been extensively studied and proven to be efficacious in the management of neonatal respiratory disorders, although use is associated with many short and long-term side effects. Research has proven that prenatal steroids are an inexpensive, safe and highly effective way of enhancing neonatal survival, reducing morbidity, decreasing the incidence and severity of RDS, and decreasing the incidence of intra ventricular hemorrhage and necrotizing enterocolitis in babies born prematurely. Although postnatal steroids are recognized to reduce rates of BPD, usage has been more controversial due to uncertainty regarding safety. In the late 1990s, reports on long-term outcomes showed early postnatal systemic dexamethasone treatment was associated with an increased risk of abnormal neurological
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Introduction

Four preterm infants with clinical and radiologic evidence of oxygen dependence and multiple risk factors for BPD were successfully weaned from ventilator support with betamethasone rescue treatment. As pharmacological management of BPD is controversial, the clinical progress secondary to an alternative therapy to systemic dexamethasone is illustrated in the following cases.

Case series

Case 1: A female infant born prematurely via caesarian section with prolonged rupture of fetal membranes at 24 weeks gestational age with a birth weight of 610 g was admitted to the neonatal intensive care unit (NICU). The APGAR scores at birth were 6 and 9 at one and five minutes, respectively. She developed respiratory distress, she was intubated and became oxygen and ventilator dependent for more than 2 weeks and she was not able to be weaned from SIMV from the first DOL. Throughout her first two weeks of life she received surfactant therapy for RDS and failed several weaning trials from high frequency oscillatory ventilation (HFOV). On DOL 14, clinical and radiologic data were consistent with oxygen dependence; she continued to require high-frequency ventilation with increasing oxygen demands (FiO2 60 to 71%) and had multiple risk factors for developing BPD. A two-dose course of betamethasone (0.1013 mg; 0.15 mg/kg) was administered on DOL 14 and 16. Within 30 hours after betamethasone initiation, her clinical status improved remarkably (FiO2 70 to 40%) and she was successfully weaned to synchronized intermittent mechanical ventilation (SIMV) on DOL 17. She was extubated to nasal intermittent mandatory ventilation (NIMV) on day 33. She remained on NIMV through DOL 57, and was weaned to nasal cannula (NC) on DOL 63. The remainder of the infant’s hospital course was unremarkable; she remained on NC as of DOL 64.

Case 2: A male infant born prematurely via caesarian section secondary to pre-eclampsia at 29 weeks gestational age with a birth weight of 1020 g was admitted to the NICU. The APGAR scores at birth were 6 and 9 at one and five minutes, respectively. He developed respiratory distress and was placed on NIMV in the delivery room. He also received surfactant therapy for RDS. On DOL 3 he was intubated and placed on HFOV due to increasing oxygen demands (FiO2 30 to 65%). On DOL 5 he was weaned to SIMV. He failed several weaning trials over the next few days with increasing oxygen demands (FiO2 30 to 50%) and a chest x-ray revealed bilateral haziness. By DOL 16, clinical and radiologic data were consistent with oxygen dependence and he had multiple risk factors for developing BPD. He was initiated on a three-day course of betamethasone (0.1815mg; 0.15 mg/kg) with doses administered on days 16, 17 and 18. Within 30 hours after betamethasone initiation, his clinical status improved remarkably and he was successfully extubated on NIMV (DOL 18).

Case 3: A female infant born prematurely via vaginal delivery with prolonged rupture of fetal membranes at 26 weeks gestational age with a birth weight of 800 g. She was admitted to the NICU. The APGAR scores at birth were 6 and 8 at one and five minutes, respectively. She developed respiratory distress, was intubated and placed on SIMV in the delivery room. She received surfactant therapy for RDS and failed several weaning trials throughout her first two weeks of...
life, with increasing oxygen demands (FiO2 30 to 37%). On DOL 17, clinical, arterial blood gases and radiologic data were consistent with ventilator and oxygen dependence and she had multiple risk factors for developing BPD. The infant was administered one dose of betamethasone (0.087 mg; 0.1mg/kg) followed by a second dose on DOL 18. Within 48 hours after betamethasone initiation, her clinical status had improved remarkably and she was successfully extubated on NIMV. A three-dose course of betamethasone therapy was completed on DOL 19. The remainder of the infant’s hospital course was unremarkable and she was discharged on DOL 52.

Case 4: A male infant born prematurely via caesarian section at 23 weeks gestational age with a birth weight of 695 g was admitted to the NICU. The APGAR score at birth was 5 at one minute. He developed respiratory distress, was intubated and placed on HFOV. Throughout his first 10 DOL he received surfactant therapy for RDS and he failed several weaning trials from HFOV. On DOL 10, his CXR revealed cystic disease and he was started on dexamethasone tapering for 10 days. On DOL 15 he developed a tension pneumothorax and a chest tube was placed. The course of dexamethasone was completed on DOL 20. Subsequently, he failed several more weaning trials remaining on HFOV (FiO2 40%) through DOL 41. He was weaned to SIMV on DOL 42. On DOL 47 he was extubated on NIMV. However, on DOL 52 he desaturated and required increased oxygen requirements. Clinical, arterial blood gases and radiologic data were consistent with ventilator and oxygen dependence. There was suspicion of CLD. A dose of betamethasone ([0.17mg;] 0.15 mg/kg) was administered, with repeated doses administered on days 53 and 54. Within 24 hours after betamethasone initiation, his clinical status improved remarkably. He was eventually weaned to nasal continuous positive airway pressure (NCPAP) on DOL 80, high-frequency nasal cannula (HFNC) on DOL 87, NC on DOL 94, and finally room air on DOL 104. The remainder of the infant’s hospital course was unremarkable and he was discharged on DOL 138 (Table 1).

### Table 1 Demographics and variables

| Infant (n=4) | Gestational age and birth weight | Sex | Betamethasone: Initiation age and doses | Ventilatory support | Time to weaning (hours after betamethasone initiation) |
|-------------|----------------------------------|-----|----------------------------------------|---------------------|-----------------------------------------------------|
| 1           | 24 wk – 610g                     | F   | DOL 14 –2                               | HFOV                | 30                                                  |
| 2           | 29 wk – 1020g                    | M   | DOL 16 –3                               | SIMV                | 30                                                  |
| 3           | 26 wk – 800g                     | F   | DOL 17 –3                               | SIMV                | 48                                                  |
| 4           | 23 wk – 695g                     | M   | DOL 52 –3                               | NIMV                | 24                                                  |

### Discussion

This case series describes postnatal use of betamethasone in four premature infants at high risk for developing BPD. We show that a short-course (2-3 days) and low-dose betamethasone therapy is associated with successful weaning from ventilator support in the NICU at DCH. Following therapy initiation, all four infants were weaned from ventilator support within 24-48 hours. BPD is the most common neonatal complication following extremely preterm birth (<28 weeks gestational age) or in extremely low birth weight (ELBW) (<1000g) infants treated with oxygen and positive pressure ventilation. Approximately half of these infants will require supplemental oxygen at 36 weeks postmenstrual age. High oxygen concentrations appear to be one of the major causative factors leading to progressive lung disease. Therefore, it is important to wean preterm infants from mechanical ventilation and to extubated them as early as possible in order to limit the progression of BPD and its associated long-term disabilities. In the 1980s, researchers identified a high incidence of BPD in babies born prematurely. Subsequently, the New England Journal of Medicine published results from a large study that associated administration of a 40-day course of postnatal dexamethasone to premature neonates with a significant decrease in length of ventilation. Several follow-up studies have supported that postnatal steroids reduce the time it takes to wean from mechanical ventilation and may help prevent the development of BPD. Following development of concern about adverse long-term neuro developmental outcomes, there was a rapid decline in the use of postnatal dexamethasone and an increase in prevalence of BPD. In spite of cautionary statements, postnatal steroids still ordered by about 40% of neonatologists both in the United States and Europe used as an attempt to wean infants from ventilator support after unsuccessful weaning trials. Therefore, there is an important need for a safe and efficacious steroid preparation and optimal dosing regimen for premature infants at risk for BPD. Effects of steroids differ with respect to preparation, dose, duration and effects on the state of end-organ maturation. The problem surrounds the short and long-term side effects associated with use of conventional high-dose long-duration dexamethasone. A 2014 systematic review suggested that use of postnatal steroids after DOL 7 may reduce neonatal mortality without increasing the risk of long-term neurological disability; however, the power of any of the included studies to demonstrate safety was limited. Attempts to study lower doses of dexamethasone, seemingly as effective as higher doses investigated, have failed to date due to under recruitment, even though many clinicians now use such a regimen. Several groups have also published small reports of short courses of hydrocortisone, and anecdotally claim it to be as effective, but this use is not based on robust trial evidence. If we can limit the systemic side effects while utilizing the local anti-inflammatory effects on the lung, steroids could be very useful in the management of BPD. Due to its high-potency, an advantage of using betamethasone is that fewer doses are required which could decrease the risk of associated side effects.

Three of our patients were ELBW neonates born extremely preterm, while the other patient was a very low birth weight (VLBW) (~1500 g) neonate born very preterm (28-31 weeks gestational age). All four patients became oxygen dependent by the end of the second week of life, required positive-pressure ventilation on or beyond DOL 10, received >40% fraction inspired oxygen (FiO2 – expressed as per cent), and exhibited either a lack of weaning or an escalation in FiO2 >10% over a 3-day period. Lack of weaning was defined as a failure to reduce FiO2 by >10% over 3 days while remaining within our predefined oxygen saturation targets. A clinically significant episode of bronchopulmonary dysplasia to assist weaning from ventilator support: a case series.
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A multicenter randomized controlled clinical trial comparing the individual steroids, dosage, timing and duration of treatment would be helpful in determining ideal postnatal steroid regimens.

Disclosures

Neither author has anything to disclose regarding this case series.

Acknowledgments

None.

Conflict of interest

The author declares there is no conflict of interest.

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Conclusion

The incidence of morbidity and mortality related to BPD in infants born prematurely is sufficiently high as to warrant consideration of corticosteroid protocols to assist in weaning from ventilator support. Studies using dexamethasone or hydrocortisone have been associated with significant short and long term side-effects. In this study, a treatment protocol using a short-course of intermittent, low-potency, intramuscular betamethasone after two weeks of life was found to be beneficial in assisting with weaning from mechanical ventilation in infants born prematurely. Before generalizations can be made as to the safety and efficacy, further studies of the use of postnatal betamethasone in this high-risk population are required. Furthermore, decrease in FiO2 was defined as a reduction of at least 20% for >24 hours. All four infants were having difficulty weaning from ventilator support after DOL 14 and received betamethasone 0.1-0.15mg/kg per day intramuscularly once per day for 2-3 days, alone or following a 10-day course of a dexamethasone taper (DART protocol). Treatment with a 2-3 times lower cortisol-equivalent dose of steroids using betamethasone resulted in an overall exposure of 0.3-0.45mg/kg over 3 days, as compared to an overall dexamethasone exposure of 0.89mg/kg over 7 days with the DART protocol. Significant reduction in FiO2 occurred within 2 days of betamethasone initiation in three of the four patients.

Along with this rescue approach for infants with established severe respiratory disease, other investigators have studied the use of early postnatal steroids in 2 situations: to prevent BPD and to reverse hypotension. Most of the published studies have been too small to determine safety, even if they provided long-term outcome data. Few trials have reported outcomes beyond 2 years, yet there is evidence of potential long-term harm in the 2 largest trials conducted in the late 1990s, both using dexamethasone as either a 3-or 28-day course. Determining long-term safety is often forgotten in the design of neonatal trials, but it is of utmost importance. Most recently, results from the largest investigation of early low-dose hydrocortisone to prevent BPD are reassuring detailing safety outcomes at 2 years of age. Although promising, the value of these results remain unclear until similar ongoing trials are completed. A limitation of this case series is that the frequency of adverse effects secondary to postnatal betamethasone use was not documented. However, the safety (better) and efficacy (same) profiles of betamethasone are encouraging compared to either high- or low-dose dexamethasone. Another major limitation of the present report is that it is a review of current practice and not a randomized controlled trial (no comparator groups for analysis). The goal of this case series is to highlight the benefits of postnatal betamethasone as an alternative to dexamethasone to assist weaning from mechanical ventilation in preterm infants at high risk for BPD. At DCH (DCH Regional Medical Center/DCH Northport Medical Center), intramuscular betamethasone has been used as an alternative to systemic dexamethasone and hydrocortisone to assist weaning from ventilator support in infants at highest risk for CLD after DOL 14 since the early 1990s. The logical extension of these results is to compare postnatal betamethasone to reduced-dose dexamethasone or hydrocortisone and placebo for facilitation of ventilator weaning. We recommend postnatal betamethasone use to be studied in a multicenter trial to investigate the improved benefits and decreased side effects of steroids in this very high-risk population of infants.
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