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Case Series

Budesonide nebulization in preterm neonates with evolving brochopulmonary dysplasia after 14 days of life: a case series

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ABSTRACT

Bronchopulmonary dysplasia (BPD) with oxygen dependence at 36 weeks postmenstrual age (PMA), remains an important complication of premature newborns. BPD occurs due to pulmonary inflammation. Reducing pulmonary inflammation with postnatal systemic corticosteroids reduces the incidence of BPD but is associated with an increased risk of long and short-term side effects. Local administration of corticosteroids via inhalation might be an effective and safe alternative. Currently, there is no recommendation for use of inhaled corticosteroids in neonatal respiratory care. However, it is being used in neonatal intensive care units (NICU) across the world in ventilator and oxygen-dependent babies. We shared our experience with the use of inhaled budesonide on nine ventilator-dependent very low birth weight (VLBW) preterm neonates in the form of case series and review the literature.

Keywords: Bronchopulmonary dysplasia, Oxygen, Newborn, Inflammation, Corticosteroids, Inhalation

INTRODUCTION

BPD, also referred to as chronic lung disease of prematurity, is the most common chronic lung disease of childhood. BPD, defined as oxygen dependency at 36 weeks PMA, has an incidence of 23% in infants born at 28 weeks and increasing to 73% in infants born at 23 weeks.[1] It is associated with prolonged respiratory support, compromised lung function and recurrent respiratory infections, eventually affecting the quality of life.[2] Furthermore, BPD is considered an independent risk factor for neurodevelopmental impairment.[3] Thus, prevention and treatment of BPD are of utmost importance in the management of preterm neonates. Pulmonary inflammation plays a central role in the pathogenesis of BPD.[4] Reducing pulmonary inflammation with postnatal systemic corticosteroids decreases the incidence of BPD in preterm infants but may be associated with an increased risk of adverse neurodevelopmental outcomes. Local administration of corticosteroids via inhalation might be an effective and safe alternative.[5] However, despite the Cochrane evidence not supporting the regular use of inhaled corticosteroids for BPD, several studies published demonstrate the widespread use of these medications in neonatal units in North America, Europe and East Asia in routine clinical care.

CASE SERIES

The patients reported in this study were admitted at NICU at Government Rajaji hospital, Madurai during the period of February 2019 to April 2020. The inclusion criteria were preterm VLBW neonates who were ventilator dependent with>0.4 (40%) Fio2 requirement on postnatal day 14 with X-ray showing features of evolving BPD. The exclusion criteria were neonates born<28 weeks, who received the bag and mask resuscitation and intubation at birth, 5 minutes Apgar less than 7,

neonates with refractory shock, neonates with suspected ventilator-associated pneumonia, associated major congenital anomaly.

Procedure

After informed consent, budesonide nebulization 500 micrograms 12 hourly was administered. The nebulizer kit supplied with a pneumovent ventilator was inserted in the inspiratory limb of the breathing circuit of the ventilator. Following extubation, budesonide nebulization was continued using a face mask with oxygen through electric jet nebulization for 7 days.

We followed written neonatal ventilation protocol in our unit. SIMV (synchronized intermittent mandatory ventilation) was the preferred invasive mode of ventilation for all neonates. The neonates who met the extubation criteria were weaned to CPAP. Once neonates reached CPAP pressure of 4 and Fio2 0.25%, they were weaned to low flow oxygen prongs or room air based on individual basis.

Outcomes

The primary outcome was BPD at 36 weeks of life. BPD was defined as the requirement for positive-pressure support or supplemental oxygen at a fraction of inspired oxygen exceeding 0.30 or in infants receiving low amounts of oxygen, fails on a structured oxygen reduction test (<90% saturation on a structured attempt to wean to ambient room air).

The other primary outcome was death at 36 weeks of PMA. Secondary outcomes were time to extubation after inhaled steroids, time to wean to room air, complications like hyperglycemia needing insulin treatment, hypertension needing medications, electrolyte imbalance, feed intolerance, sepsis, oral candidiasis and intracranial haemorrhage, growth and development following discharge till one year of corrected gestational age.

Results

Tables 1 and 2 show the characteristics of neonates. There were 3 male and 6 female neonates. The mean birth weight of neonates was 1395.55±80.64 grams and mean gestation was 31.04±0.43 weeks and all were appropriate for gestational age. In our neonates 4 mothers had preeclampsia, 2 had gestational diabetes mellitus well controlled with diet and 3 mothers had no antenatal complications. No other significant antenatal complications were present in mothers and all mothers had regular antenatal visits with normal antenatal scans. All mothers received antenatal steroid dexamethasone, 3 doses in six mothers and 4 doses in three mothers. In our case, seven neonates required 2 doses and two neonates required 1 dose of surfactant. All neonates were started on gavage feeds from day 1 of life and gradually increased. Bedside echo after 24 hours was normal for all neonates.

There was no death at 36 weeks of life and none of the neonates developed BPD. All the neonates were extubated to nasal ventilator CPAP within 7 days of starting budesonide. Mean extubation time was 5±0.707 days after initiation of nebulization (Table 2). The mean duration of nasal CPAP therapy in our neonates was 37.556±3.087 hours following extubation (Table 2). From CPAP the neonates were weaned to low flow nasal prongs oxygen. The mean duration of nasal prongs oxygen was 33.66±12.85 hours. Mean time to wean to room air was at 22.33±0.50 postnasal days (Table 2). Once weaned to room air none of the neonates required repeat oxygen therapy or respiratory support. At 28 days of life and 36 weeks of postmenstrual age, all our neonates were in room air.

Table 1: Baseline characteristics.

Sr. No.	Birth weight (in grams)	Gestation at birth (in weeks)	Sex	Maternal complications	Antenatal steroid dose	Surfactant doses
1.	1410	30 6/7	Male	Preeclampsia	3	2
2.	1470	31 2/7	Male	Preeclampsia	4	2
3.	1270	30 3/7	Female	GDM	3	2
4.	1290	31	Female	Preeclampsia	3	2
5.	1400	31 4/7	Female	Nil	3	2
6.	1360	30 6/7	Female	Preeclampsia	4	2
7.	1490	315/7	Female	Nil	3	1
8.	1380	30 4/7	Female	GDM	3	2
9.	1490	31 1/7	Male	Nil	4	1
Mean	1395.56	31.044			3.3	1.77
SD	80.64	0.43				

Table 2: Outcomes.

Sr. No.	Time to extubation (in days)*	Time to extubation (in hours)*	CPAP duration (in hours)	Nasal O_2 prongs duration (in hours)	Time to wean to room air (PND)	Death	Day 28 oxygen dependent	36 weeks PMA O_2 requirement
1.	5	116	38	48	23	Nil	No	No
2.	6	140	38	24	23	Nil	No	No
3.	4	90	40	44	22	Nil	No	No
4.	5	110	32	36	22	Nil	No	No
5.	5	115	36	43	23	Nil	No	No
6.	6	138	39	6	22	Nil	No	No
7.	5	109	42	30	22	Nil	No	No
8.	5	115	34	32	22	Nil	No	No
9.	4	95	39	40	22	Nil	No	No
Mean	5	114.22	37.56	33.66	22.33			
SD	0.707	16.717	3.087	12.85	0.50			

*Time after commencing budesonide nebulisation; PND - Postnatal days, PMA- postmenstrual age, O2- oxygen.

No prespecified complications outlined in secondary outcomes were noted in the study neonates after intervention. Neurosonograms and echo were normal. ROP and BERA were normal for all neonates. There was no history of recurrent respiratory tract infection or hospital admissions. Last anthropometry, developmental assessment using Trivandrum screening test, neurological and other systemic examination done at 1 year corrected gestational age were normal for all neonates.

DISCUSSION

In 1967, Northway coined the term BPD for the gradual development of pulmonary disease in premature neonates that had experienced respiratory distress syndrome (RDS) upon birth. Northway et al defined and categorized radiologic criteria for this pulmonary disease and attributed its development process to the exposure of a premature lung to oxygen and mechanical ventilation. BPD is a multifactorial disease with mechanical ventilation, oxygen toxicity and pre and postnatal infection as the most important risk factors and pulmonary inflammation playing a central mediating role.

Corticosteroids with their strong anti-inflammatory effect can attenuate the inflammatory response associated with BPD. Randomized controlled trials (RCTs) have shown that systemic administration of corticosteroids reduces the incidence of BPD and the combined outcome of death or BPD in ventilated preterm infants.[6] Systemic corticosteroids were also associated with short-term (hyperglycemia, hypertension, infection) and long-term (neurodevelopmental impairment) adverse effects.[7] Inhaled corticosteroids demonstrated high pulmonary deposition in addition to low systemic bioavailability and rapid systemic clearance, thus providing a safe and effective alternative to systemic steroids. Budesonide, beclomethasone and fluticasone were the most frequently used inhaled corticosteroids in neonates and these drugs were almost exclusively delivered using a pressurized metered-dose inhaler or a nebulizer.[8]

Metanalysis by Shinwell et al concluded that very preterm infants appeared to benefit from inhaled corticosteroids with reduced risk for BPD and no effect on death, other morbidities or adverse events.[9] Cochrane database of systematic reviews 2017 concluded that inhalation corticosteroids initiated at ≥7 days of life for preterm infants at high risk of developing BPD cannot be recommended as there was statistical heterogeneity because trials used different drugs, dosages and delivery systems.[10] They recommended further studies for conclusive evidence.

In a questionnaire that was sent to pediatricians-in-chief of 223 German pediatric hospitals approximately 50% administered inhaled corticosteroids to premature infants either as a prophylaxis or treatment for BPD.[11] According to a national survey in the UK, 22% of the units reported that they sometimes used inhaled corticosteroids to facilitate extubation of ventilator-dependent babies with evolving or established BPD.[12] In the USA, a retrospective COHORT study of 1429 infants with evolving BPD revealed, that inhaled corticosteroids were prescribed to 25% of the COHORT with use steadily increasing during the first two months of hospitalization.[13] Finally, a questionnaire that was sent to all 96 tertiary neonatal units in Japan showed that inhaled corticosteroids were used approximately 70% for the prevention and treatment of BPD.[9] Budesonide was the popular drug in all the studies.[14] These surveys showed that inhaled corticosteroids were widely used for the prevention or treatment of BPD in preterm infants in clinical practice despite lack of evidence.

In a large trial (NEUROSIS) Bassler et al found that in extremely preterm neonates treated within 24 hours after birth with inhaled budesonide the incidence of bronchopulmonary dysplasia was lower but a significant increase in mortality was also reported in the budesonide group.[5] But in our protocol, the study population was of higher gestational age and inhaled budesonide was given for the most at risk babies who were ventilator-dependent at 14 days of life. This excluded neonates on oxygen prongs and CPAP who may have a higher chance of weaning to room air even without budesonide.

We found that all our neonates tolerated extubation well after starting budesonide nebulization (mean extubation time 5±0.707 days) similar to Jonsson et al study.[15] In our case, all 9 neonates were weaned to room air before 28 days of life. This was in opposition to Jonsson et al study where all the neonates required supplemental oxygen at 28 days of age. All our neonates remained in room air at 36 weeks of PMA. As per Jonsson et al trial 61% of infants in the budesonide group needed supplemental oxygen versus 79% of infants in the placebo group at 36 weeks of PMA.[15] Two other controlled trials have demonstrated speedy extubation after nebulized dexamethasone or beclomethasone dipropionate.[16,17]

The limitations in our present study were that there was no control group, the extreme preterm neonates who were more vulnerable for BPD were excluded because of high mortality in that age group in our unit. The other limitations were that the neonates requiring lesser support like CPAP or oxygen prongs on postnatal day 14 were not studied. Long-term outcomes using a detailed developmental assessment scale like Bayley were not used. Higher cognitive functions were not assessed at 1 year and need further follow up. In an actual situation, neonates with BPD would have other co-morbidities and we excluded these babies. The efficacy of budesonide nebulization in these babies was not studied.

CONCLUSION

In our small case series, we found that all the neonates were benefitted from inhaled budesonide therapy without any systemic complications. Inhaled budesonide therapy can be a safe option in ventilator-dependent preterm neonates >28 weeks, at 14 days of postnatal life with evolving BPD. We conclude that large RCTs are needed to reach a final consensus and to recommend the use of inhaled steroids in preterm prolonged ventilator-dependent neonates with short and long-term safety.

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