ORIGINAL RESEARCH PAPER

Paediatrics

KEY WORDS:
Bronchopulmonary Dysplasia, Preterm Neonate, Dexamethasone, Budesonide, Formoterol, Mechanical Ventilation

EFFECT OF COMBINED LOW-DOSE SYSTEMIC CORTICOSTEROID AND INHALATIONAL THERAPY ON RESPIRATORY OUTCOMES IN PRETERM NEONATES WITH BRONCHOPULMONARY DYSPLASIA IN A TERTIARY CARE CENTRE

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ABSTRACT

Background: Bronchopulmonary dysplasia (BPD) is a major cause of morbidity and mortality in extremely preterm neonates requiring prolonged invasive ventilation and oxygen support3. The combined early use of systemic corticosteroids and inhalational corticosteroid–bronchodilator therapy may reduce inflammation, improve lung compliance, and shorten ventilation duration1-2. **Objective:** To evaluate the effect of early versus delayed initiation of low-dose systemic dexamethasone and combined inhaled budesonide–formoterol therapy on respiratory outcomes among preterm neonates diagnosed with evolving BPD. **Methods:** A prospective observational study was conducted in the Neonatal Intensive Care Unit (NICU) at Hi-Tech Medical College & Hospital, Bhubaneswar from January 2024 – October 2025. A total of 148 neonates <32 weeks gestation and ≤1500 g birth weight were enrolled: 88 inborn and 60 outborn infants. Inborn infants received early DART regimen (<7 days) followed by inhalational therapy after extubation; outborn infants received the same regimen >14 days after birth. Statistical analysis included independent t-tests and chi-square tests. **Results:** Mean time to extubation was significantly shorter in inborn neonates (3–6 days; mean 4.2 ±0.8) compared to outborn infants (4–10 days; mean 7.0 ±1.5) ($p<0.001$). Oxygen dependency duration was significantly lower in inborn infants (10–20 days; mean 15.0 ±2.5) versus outborn (18–45 days; mean 29.0 ±6.8) ($p<0.001$). Successful ventilator weaning was higher in inborn infants (93.1%) versus outborn (71.6%) ($\chi^2=12.41$, $p=0.0004$). Mortality was lower among inborn (6.8%) than outborn infants (18.3%) ($p=0.03$). **Conclusion:** Early initiation of low-dose systemic dexamethasone combined with inhaled budesonide and formoterol significantly improves respiratory outcomes, accelerates weaning from mechanical ventilation and oxygen dependency, and reduces mortality. Standardized early intervention protocols may reduce progression to severe BPD.

INTRODUCTION

Bronchopulmonary dysplasia remains a major cause of morbidity in extremely preterm neonates despite advances in neonatal ventilation and respiratory support strategies. BPD is defined as persistent oxygen dependency at 36 weeks post-menstrual age or ≥28 days postnatal age[3]. Premature infants <32 weeks are at high risk due to lung immaturity and exposure to mechanical ventilation, oxygen-induced oxidative stress, airway inflammation, barotrauma, volutrauma, and infection-mediated cytokine injury[3-8].

The pathophysiology of BPD is characterized by disrupted alveolarization, inflammatory cytokine activation, impaired angiogenesis, and fibrosis[11-12]. Studies have demonstrated elevated levels of IL-6, IL-8, TNF-α and neutrophil influx into the pulmonary tissue of infants who subsequently develop BPD[12]. Persistent inflammation leads to reduced lung compliance, atelectasis, prolonged ventilation dependence, and late pulmonary sequelae including pulmonary hypertension and recurrent wheezing[11].

Systemic corticosteroids such as dexamethasone have potent anti-inflammatory effects that improve lung compliance and facilitate extubation. The DART trial demonstrated improved extubation success with low-dose dexamethasone while avoiding neurodevelopmental toxicity associated with earlier high-dose regimens[1]. Inhaled corticosteroids such as budesonide allow targeted pulmonary anti-inflammatory action with fewer systemic effects[6]. Combination bronchodilator therapy using formoterol enhances airway smooth muscle relaxation and improves lung mechanics[11].

The NEUROSIS trial demonstrated significant reduction in BPD incidence among extremely low birth weight infants using early inhaled budesonide therapy, although concerns regarding mortality and long-term neurodevelopment persist[2]. Recent studies suggest combined therapy may optimize outcomes, yet evidence regarding timing of initiation remains limited, especially in Indian resource-limited NICU settings where late referrals and transport instability may worsen outcomes[4-5].

The present study evaluates early versus late initiation of systemic corticosteroid and inhalational therapy in preterm neonates with evolving BPD.

Objectives

1. To compare respiratory outcomes between inborn neonates receiving early combined therapy and outborn neonates receiving delayed therapy.
2. To evaluate effects of combined inhalational budesonide and bronchodilator on oxygen dependency and weaning success.
3. To determine mortality and short-term clinical improvement following therapy.

MATERIALS AND METHODS

Study Design: Prospective observational study.
Study Setting and Duration: NICU, Hi-Tech Medical College & Hospital, Bhubaneswar (January 2024 – October 2025)
Sample Size: 148 neonates with evolving BPD(88 inborn, 60 outborn)

Inclusion Criteria

- <32 weeks gestation
- Birth weight ≤1500 g
- Mechanical ventilation >5 days or NIV with FiO_2 > 30%

Exclusion Criteria

- Major congenital malformations
- Sepsis
- Refusal of consent

Treatment Protocol

Systemic Therapy: DART regimen (Low-dose IV

dexamethasone x 10 days)
Inhalational Therapy: MDI Budesonide 100 mcg + Formoterol 6 mcg twice daily post-extubation

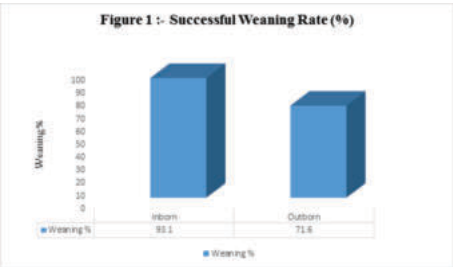
Outcome Measures
- Time to successful extubation
- Duration of oxygen dependency
- Weaning success
- Mortality

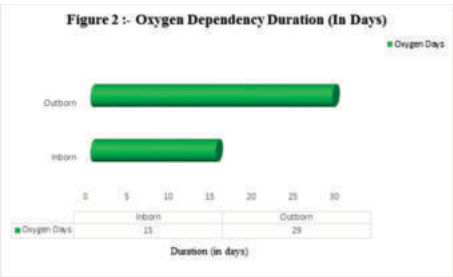
Ethical Statement
Ethical approval was obtained from the Institutional Ethics Committee of Hi-Tech Medical College and Hospital, Bhubaneswar.

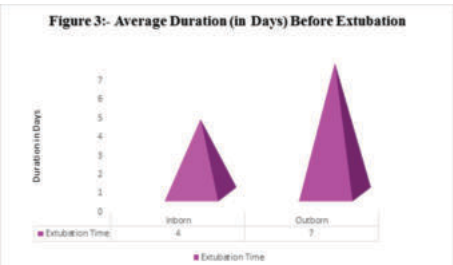
Statistical Analysis
SPSS v26.0. Independent t-test for continuous variables. Chi-square test for categorical variables. Significance $p < 0.05$.

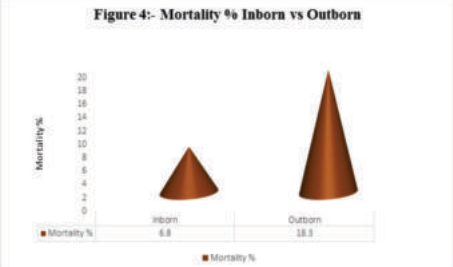
RESULTS
Table 1: Comparison of Clinical Outcomes Between Groups

Outcome	Inborn (n=88)	Outborn (n=60)	p-value
Time to extubation (mean ± SD)	4.2 ± 0.8 days	7.0 ± 1.5 days	<0.001
Oxygen dependency duration	15.0 ± 2.5 days	29.0 ± 6.8 days	<0.001
Successful weaning	82 (93.1%)	43 (71.6%)	0.0004
Mortality	6 (6.8%)	11 (18.3%)	0.03









DISCUSSION
The present study demonstrates that early initiation of systemic corticosteroid and inhaled budesonide–formoterol significantly improves respiratory outcomes in extremely preterm infants with evolving BPD. Early therapy reduced inflaammation, enhanced lung compliance, accelerated ventilator weaning, and shortened oxygen dependency compared with delayed therapy in outborn infants.

Our findings are consistent with the DART trial (Doyle et al.), which showed that low-dose dexamethasone significantly improves extubation capacity[1]. Similarly, Bassler et al. demonstrated improved respiratory outcomes with early inhaled budesonide in the NEUROSIS trial[2]. The marked difference in outcomes between inborn and outborn neonates likely reflects the compounding effect of delayed therapy initiation combined with transport related physiological stress and potential deterioration during transfer.

The 40% reduction in extubation time observed in our inborn cohort (4.2 vs 7.0 days) is clinically significant, as each additional day of mechanical ventilation increases the risk of ventilator-associated complications including infection, barotrauma, and further lung injury. The substantial reduction in oxygen dependency duration (15 vs 29 days) translates to shorter NICU stays, reduced healthcare costs, and earlier parent-infant bonding opportunities.

The weaning success rate of 93.1% in inborn neonates compared to 71.6% in outborn infants underscores the importance of timely intervention. Failed extubation attempts are associated with increased morbidity, prolonged hospitalization, and higher mortality rates. Our data suggest that standardized early intervention protocols could significantly reduce these adverse outcomes.

Mortality was significantly lower among inborn infants (6.8% vs 18.3%), highlighting the importance of early respiratory management and the detrimental effects of delayed treatment initiation. This finding aligns with recent meta-analyses suggesting that steroid benefit is greatest in high-risk preterm infants when initiated appropriately[10].

The combination of systemic dexamethasone with inhaled budesonide and formoterol represents a dual-action approach: systemic anti-inflammatory effects combined with targeted pulmonary drug delivery[11]. The bronchodilator component (formoterol) may provide additional benefit through improved airway patency and enhanced drug distribution within the developing lung.

Our results support the growing body of evidence favoring early, protocol-driven steroid therapy in evolving BPD[14-15]. However, the study also highlights the challenges faced by outborn neonates in resource-limited settings, where delayed referrals and transport instability may compromise outcomes despite optimal treatment once admitted

CONCLUSION
Early administration of low-dose systemic dexamethasone combined with inhalational budesonide and formoterol significantly reduces mechanical ventilation duration, oxygen dependency, and mortality in preterm neonates with evolving BPD. Standardized early therapy should be considered in NICUs to optimize respiratory outcomes and prevent progression to severe BPD.

Limitations
- Single-center study
- Short-term follow-up only
- No neurodevelopmental outcome evaluation
- Observational study; potential selection bias between inborn and outborn groups

Future Scope

- Multi-center randomized controlled trials are required
- Long-term neurodevelopmental follow-up should be evaluated
- Comparison of inhalational vs intratracheal steroid delivery techniques
- Cost-effectiveness analysis of early intervention protocols

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