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Hydrocortisone Versus Dexamethasone Initiated in the Second Postnatal Week in Preterm Neonates at Risk of Bronchopulmonary Dysplasia: A Retrospective Exploratory Comparative Study

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Abstract

Background: Bronchopulmonary dysplasia (BPD) is a major cause of mortality and of long-term respiratory morbidity in preterm neonates, and inflammation is central to its pathogenesis. Corticosteroids are widely used for its prevention and treatment, but direct head-to-head comparisons of hydrocortisone and dexamethasone are limited. This exploratory study compared the two agents. Its primary objective was to compare death or BPD at 36 weeks postmenstrual age (PMA) in preterm neonates born at or before 34 weeks of gestation who received hydrocortisone or dexamethasone in the second postnatal week for evolving lung disease, and its secondary objectives were to compare respiratory weaning, duration of support and short-term safety.

Methodology: In this retrospective comparative observational study, the records of preterm neonates born at or before 34 weeks of gestation and admitted to a tertiary-care neonatal intensive care unit (NICU) in western India between October 2022 and April 2024, who required respiratory support during the second week of life and received either hydrocortisone or low-dose dexamethasone, were reviewed. Hydrocortisone was given as 1 mg/kg/day for seven days followed by 0.5 mg/kg/day for three days, and dexamethasone as a low-dose regimen with a cumulative dose of 0.89 mg/kg over 10 days. The primary outcome was death or BPD at 36 weeks PMA. Secondary outcomes were weaning from respiratory support, duration of ventilation and of hospital stay, and short-term adverse events. Categorical data were compared using the chi-square test or, for sparse data, Fisher's exact test. Data were analyzed by intention to treat using SPSS Statistics version 22.0 (IBM Corp., Armonk, NY, USA), and all comparisons were treated as exploratory.

Results: Of 37 neonates, 18 received hydrocortisone and 19 received dexamethasone, and baseline neonatal and maternal characteristics were comparable. Weaning from oxygen support (66.7% versus 73.7%, p = 0.641), BPD at 36 weeks PMA (16.7% versus 0%) and death at 36 weeks PMA (5.6% versus 10.5%) did not differ significantly, and the composite of death or BPD did not differ significantly (22.2% versus 10.5%, Fisher's exact p = 0.405; risk difference 11.7%, 95% CI −12.0% to 35.3%). The total duration of ventilation was shorter in the dexamethasone group (15.8 versus 19.1 days, t(35) = 2.17, p = 0.037; not significant after Bonferroni correction), whereas the duration of hospital stay (34.7 versus 29.1 days, t(35) = 1.39, p = 0.173) and the frequency of each short-term adverse event were comparable.

Conclusions: In this small, retrospective exploratory study, no statistically significant difference was detected between hydrocortisone and dexamethasone initiated during the second postnatal week in death or BPD at 36 weeks PMA, respiratory weaning or short-term adverse events. Equivalence cannot be inferred. The wide confidence interval around the primary outcome is compatible with clinically important differences in either direction, so these findings are hypothesis-generating and require confirmation in adequately powered randomized trials with long-term neurodevelopmental follow-up.

Categories: Orthopedics
Keywords: bronchopulmonary dysplasia, dexamethasone, hydrocortisone, neonatal intensive care, postnatal corticosteroids, preterm neonate, respiratory outcomes, weaning from ventilation

Introduction

Bronchopulmonary dysplasia (BPD) remains a leading cause of mortality and of long-term respiratory and neurodevelopmental morbidity in extremely preterm infants [1]. First described in ventilated infants with hyaline membrane disease, BPD persists despite modern, gentler ventilation, largely because of the improved survival of the most immature infants, in whom ventilator-induced injury, prolonged oxygen exposure, sepsis and inflammation interact [2,3]. Inflammation is central to its pathogenesis, which has long driven the use of corticosteroids for both prevention and treatment [4]. However, concern about the neurodevelopmental harm of early high-dose dexamethasone led the American Academy of Pediatrics to advise against it [5], and Cochrane reviews suggest that the benefits of corticosteroids started within the

first postnatal week may not outweigh the risks, whereas treatment after the first week may reduce mortality without clearly increasing neurodevelopmental risk [6,7]. A more physiological, low-dose hydrocortisone approach has been proposed to preserve respiratory benefit while limiting harm [8], and the Early Low-Dose Hydrocortisone to Improve Survival Without Bronchopulmonary Dysplasia in Extremely Preterm Infants (PREMILOC) trial reported improved BPD-free survival with early low-dose hydrocortisone [9]. Direct head-to-head comparisons of hydrocortisone and dexamethasone, however, remain scarce, and the optimal agent for infants who are still ventilator- or oxygen-dependent beyond the first postnatal week is therefore unresolved.

This exploratory study addressed that gap in a resource-constrained tertiary-care unit. Both agents were used for a single clinical indication: preterm neonates born at or before 34 weeks of gestation who remained dependent on respiratory support during the second postnatal week and were therefore at high risk of established BPD, so that treatment aimed to prevent established BPD in infants with evolving lung disease, rather than to provide prophylaxis from birth or to treat BPD already diagnosed at 36 weeks postmenstrual age (PMA). The primary objective was to compare the composite of death or BPD at 36 weeks PMA between the hydrocortisone and dexamethasone groups. The secondary objectives were to compare weaning from respiratory support, the duration of ventilation and of hospital stay, and short-term adverse events. Because the design was retrospective and non-randomized, the comparison was descriptive and was not designed to establish equivalence or non-inferiority.

Materials And Methods

Study design and setting

This was a retrospective comparative observational study conducted in the neonatal intensive care unit (NICU) of a tertiary-care teaching hospital in western India. The records of preterm neonates admitted between October 2022 and April 2024 were reviewed. The study was approved by the Institutional Ethics Committee (approval number SVIEC/ON/Medi/BNPG21Oct/22/59) and was conducted in accordance with the Declaration of Helsinki. Because the study was retrospective and used only routinely recorded hospital data, the Institutional Ethics Committee waived the requirement for informed consent. All case records were anonymized before data extraction; no names, hospital registration numbers, dates of birth or admission, photographs or any other potentially identifying details of the neonates or their parents were collected, and this article reports only pooled group data and contains no identifying patient information.

Participants

Inborn and outborn preterm neonates born at or before 34 weeks of gestation who required respiratory support during the second week of life were eligible. Respiratory support was defined as invasive ventilation, non-invasive ventilation (continuous positive airway pressure or high-flow nasal cannula), or oxygen therapy with a fraction of inspired oxygen (FiO2) of 25% or more. Neonates born after 34 weeks of gestation and those with congenital heart disease, chromosomal anomalies or major congenital malformations were excluded. No formal sample-size calculation determined the cohort size. Instead, all consecutive eligible neonates treated during the 19-month study period were included, so the sample size was fixed by the number of available records, and the study was not powered to test equivalence or non-inferiority. Of 42 neonates assessed for eligibility during the study period, five were excluded and all 37 eligible neonates were included (Figure *1*).

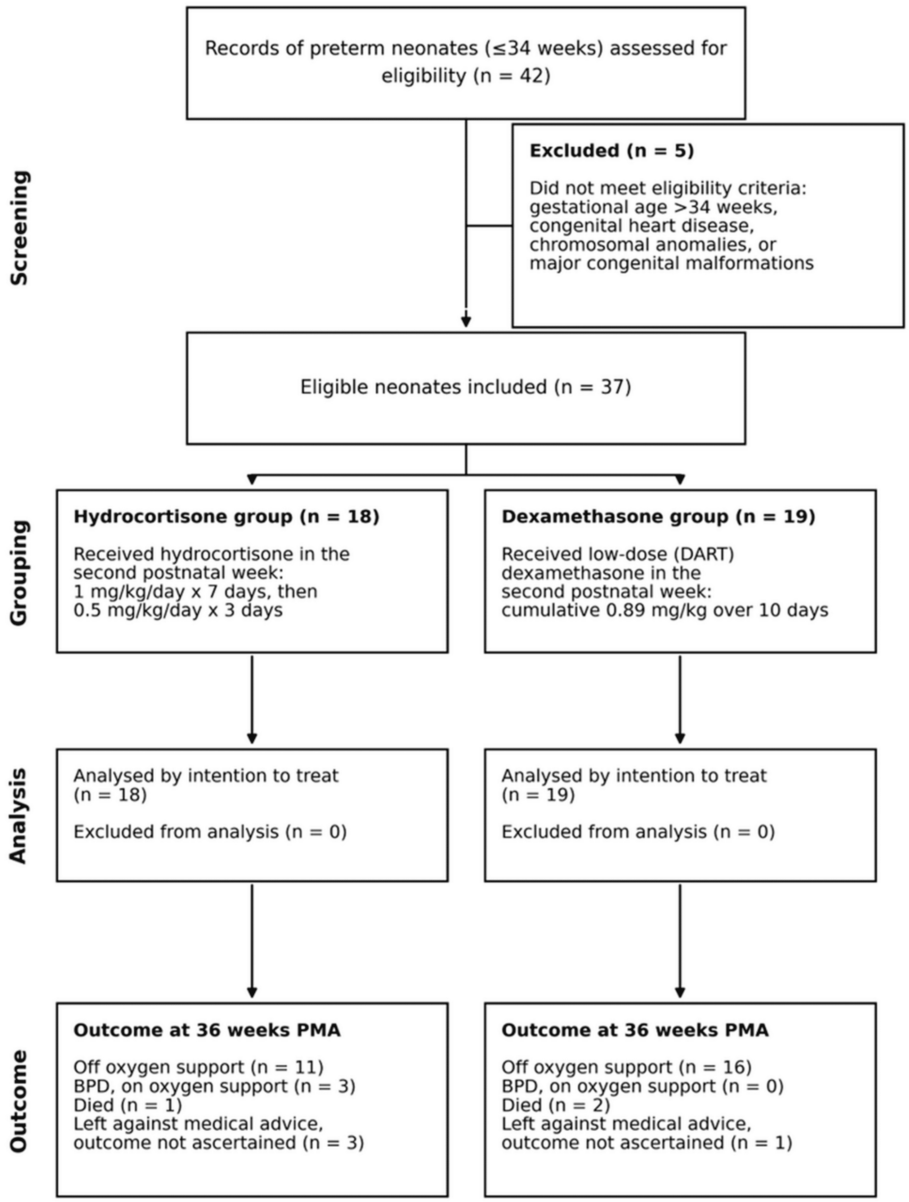


FIGURE 1: Study flow diagram

Study flow diagram showing screening, eligibility, grouping and 36-week outcomes of preterm neonates according to the corticosteroid received during the second postnatal week. Of 42 records screened, five did not meet the eligibility criteria and 37 neonates were included, 18 in the hydrocortisone group and 19 in the dexamethasone group. All 37 were retained in the intention-to-treat analysis, and none were excluded. The four outcome categories at 36 weeks postmenstrual age are mutually exclusive and sum to the number of neonates in each group (11 + 3 + 1 + 3 = 18 and 16 + 0 + 2 + 1 = 19). BPD: bronchopulmonary dysplasia; PMA: postmenstrual age; DART: Dexamethasone: A Randomised Trial. Figure created by the authors.

Groups and intervention

Eligible neonates had received either hydrocortisone or dexamethasone during the second week of life, in addition to standard care, and were grouped according to the agent received. Corticosteroid therapy was considered for neonates who still required respiratory support, as defined above, during the second postnatal week. The choice between the two agents was left to the treating neonatologist, because the unit had no written protocol favoring either drug during the study period; the reasons for each individual choice were not systematically recorded in the case files, which is a recognized source of confounding by indication. All other respiratory and supportive management, including surfactant administration, ventilation strategy and oxygen targets, followed the standard unit practice applied to all neonates. Hydrocortisone was given as 1 mg/kg/day in two divided doses for seven days, followed by 0.5 mg/kg/day for three days [9]. Dexamethasone followed a low-dose regimen based on the Dexamethasone: A Randomised Trial (DART) protocol, with a cumulative dose of 0.89 mg/kg over 10 days (0.075 mg/kg/dose 12-hourly for three days, 0.05 mg/kg/dose for

three days, 0.025 mg/kg/dose for two days and 0.01 mg/kg/dose for two days) [10]. The total duration of therapy was 10 days in both groups.

Data collection and outcomes

Maternal and antenatal history, birth details, baseline respiratory status and FiO2, mode of ventilation at trial entry and at the end of therapy, and subsequent outcomes were retrieved from case records. BPD was defined by the need for supplemental oxygen at 36 weeks PMA [11,12]. Respiratory status at 36 weeks PMA was taken from the case-record entry for that week; neonates discharged home in room air before 36 weeks PMA were classified as alive without BPD, and no physiological oxygen-reduction test was performed. The primary outcome was death or BPD at 36 weeks PMA. FiO2, the mode of respiratory support and weaning were assessed at the start and at the end of the 10-day course. Neonates who left against medical advice before 36 weeks PMA had no recorded 36-week outcome; they were retained in the intention-to-treat denominator as 'outcome not ascertained', and the effect of these missing outcomes was explored in sensitivity analyses. Secondary outcomes were weaning from any respiratory support and from oxygen, duration of ventilation and of hospital stay, and short-term adverse events (retinopathy of prematurity, necrotizing enterocolitis, intraventricular hemorrhage, patent ductus arteriosus, gastrointestinal bleeding, hypertension and hyperglycemia).

Statistical analysis

Data were analyzed using SPSS Statistics version 22.0 (IBM Corp., Armonk, NY, USA). Categorical variables were summarized as frequencies and percentages. They were compared using the Pearson chi-square test when all expected cell counts were five or more, and otherwise using Fisher's exact test, with the Fisher-Freeman-Halton extension for variables with more than two categories; exact p values and the sensitivity analyses were computed in Python using SciPy version 1.18. Continuous variables were summarized as mean plus or minus standard deviation and compared using the independent-samples Student t test. For transparency, the test statistic with its degrees of freedom, χ^2(df) or t(df), is reported in the tables beside every p value, and p values obtained from Fisher's exact test are marked with a dagger (†). The primary composite outcome was also expressed as a risk difference with a Wald 95% confidence interval (CI). Outcomes were analyzed by intention to treat, with all 37 neonates retained in the group of the agent received. Because the 36-week outcome was not ascertained in four neonates, a complete-case analysis and best-case and worst-case imputations were performed as sensitivity analyses for the primary outcome. Multivariable adjustment for confounders was not attempted, because only six primary-outcome events occurred. No correction was made for multiple comparisons, so all secondary analyses were regarded as exploratory. A two-tailed p value below 0.05 was considered statistically significant.

Results

Of the 37 neonates analyzed, 18 received hydrocortisone and 19 received dexamethasone (Figure *1*). The two groups were comparable at baseline (Table *1*). Males accounted for 56.8% of the cohort (male-to-female ratio 1.3:1). The distribution of birth weight, gestational age (28 to 32 weeks being most common in both groups) and the proportion small for gestational age (44.4% versus 26.3%) did not differ significantly. Surfactant had been administered to a similar proportion of each group (55.6% versus 52.6%).

Characteristic	Hydrocortisone (n = 18)	Dexamethasone (n = 19)	Test statistic	p-value
Male sex, n (%)	9 (50.0)	12 (63.2)	$\chi^2(1) = 0.65$	0.419
Birth weight <1 kg, n (%)	4 (22.2)	3 (15.8)	$\chi^2(3) = 1.70$	0.701†
Birth weight 1-1.5 kg, n (%)	9 (50.0)	7 (36.8)	-	-
Birth weight 1.5-2.0 kg, n (%)	4 (22.2)	8 (42.1)	-	-
Birth weight >2.0 kg, n (%)	1 (5.6)	1 (5.3)	-	-
Gestational age <28 weeks, n (%)	1 (5.6)	1 (5.3)	$\chi^2(2) = 0.02$	1.000†
Gestational age 28-32 weeks, n (%)	10 (55.6)	11 (57.9)	-	-
Gestational age >32 weeks, n (%)	7 (38.9)	7 (36.8)	-	-
Small for gestational age, n (%)	8 (44.4)	5 (26.3)	$\chi^2(1) = 1.33$	0.248
Surfactant administered, n (%)	10 (55.6)	10 (52.6)	$\chi^2(1) = 0.03$	0.858

TABLE 1: Baseline neonatal characteristics of the two groups

All variables in this table are categorical and were compared between groups using the Pearson chi-square test or, where any expected cell count was below five, Fisher's exact test (†; Fisher-Freeman-Halton extension for birth weight and gestational age); the chi-square statistic with its degrees of freedom, $\chi^2(df)$, is shown beside each p value. A dash indicates a row that forms part of a multi-category comparison, for which the test statistic and the p value are reported on the first row of that variable.

Maternal and antenatal characteristics were also similar (Table 2). The mean maternal age was 24.3 versus 22.8 years (p = 0.148). Antenatal corticosteroid coverage (55.6% versus 31.6%), pregnancy-induced hypertension, clinical chorioamnionitis (5.4% overall), premature rupture of membranes and multiparity showed no significant between-group differences; cesarean delivery was numerically more frequent in the hydrocortisone group (50.0% versus 26.3%, p = 0.138).

Characteristic	Hydrocortisone (n = 18)	Dexamethasone (n = 19)	Test statistic	p-value
Maternal age, years (mean ± SD)	24.33 ± 2.89	22.84 ± 3.22	$t(35) = 1.48$	0.148
Antenatal corticosteroids, n (%)	10 (55.6)	6 (31.6)	$\chi^2(1) = 2.17$	0.141
Pregnancy-induced hypertension, n (%)	5 (27.8)	1 (5.3)	$\chi^2(1) = 3.45$	0.090†
Clinical chorioamnionitis, n (%)	1 (5.6)	1 (5.3)	$\chi^2(1) = 0.002$	1.000†
Premature rupture of membranes, n (%)	4 (22.2)	4 (21.1)	$\chi^2(1) = 0.007$	1.000†
Multiparity, n (%)	10 (55.6)	10 (52.6)	$\chi^2(1) = 0.03$	0.858
Cesarean delivery, n (%)	9 (50.0)	5 (26.3)	$\chi^2(1) = 2.20$	0.138

TABLE 2: Maternal and antenatal characteristics of the two groups

SD: standard deviation. Categorical variables were compared using the Pearson chi-square test, $\chi^2(df)$, and maternal age using the independent-samples Student t test, t(df); each statistic is shown beside its p value. †Fisher's exact test, used because at least one expected cell count was below five.

Respiratory parameters and weaning outcomes are shown in Table 3. The mean FiO2 before therapy was comparable (26.4% versus 26.4%, p = 0.933) and did not differ at the end of therapy. Weaning from oxygen support was achieved in 66.7% versus 73.7% (p = 0.641) and weaning from the entry mode of ventilation in 83.3% versus 84.2% (Fisher's exact p = 1.000). The duration of invasive and of non-invasive ventilation did not differ; however, the total duration of ventilation was shorter in the dexamethasone group (15.8 versus 19.1 days, $t(35) = 2.17$, p = 0.037). This difference was nominal. It persisted with Welch's t test (p = 0.041) but would not remain significant after Bonferroni correction for the eight comparisons in Table 3 (adjusted threshold p < 0.006), and it should therefore be interpreted with caution.

Parameter	Hydrocortisone (n = 18)	Dexamethasone (n = 19)	Test statistic	p-value
FiO2 before therapy, % (mean ± SD)	26.44 ± 2.75	26.37 ± 2.69	t(35) = 0.08	0.933
FiO2 after therapy, % (mean ± SD)	22.61 ± 2.59	26.84 ± 16.16	t(35) = -1.10	0.280
Weaned from oxygen support, n (%)	12 (66.7)	14 (73.7)	$\chi^2(1) = 0.22$	0.641
Weaned from entry ventilation mode, n (%)	15 (83.3)	16 (84.2)	$\chi^2(1) = 0.005$	1.000†
Invasive ventilation, days (mean ± SD)	0.44 ± 1.89	0.47 ± 1.43	t(35) = -0.06	0.958
Non-invasive ventilation, days (mean ± SD)	8.11 ± 7.80	9.74 ± 7.92	t(35) = -0.63	0.534
Total ventilation, days (mean ± SD)	19.07 ± 5.51	15.80 ± 3.50	t(35) = 2.17	0.037*
Time to weaning, days (mean ± SD)	5.58 ± 2.02	4.71 ± 1.68	t(24) = 1.20	0.243

TABLE 3: Respiratory support parameters and weaning outcomes

FiO2: fraction of inspired oxygen; SD: standard deviation. *Statistically significant ($p < 0.05$). Continuous variables were compared using the independent-samples Student t test, t(df), and categorical variables using the Pearson chi-square test, χ^2(df); each statistic is shown beside its p value. Time to weaning was calculated only in the neonates who were successfully weaned (12 in the hydrocortisone group and 14 in the dexamethasone group), which accounts for the lower degrees of freedom of that comparison. †Fisher's exact test, used because at least one expected cell count was below five.

The primary and other clinical outcomes are presented in Table 4. The primary composite outcome of death or BPD at 36 weeks PMA occurred in four of 18 neonates (22.2%) in the hydrocortisone group and in two of 19 (10.5%) in the dexamethasone group ($\chi^2(1) = 0.93$, Fisher's exact p = 0.405; risk difference 11.7%, 95% CI −12.0% to 35.3%). The distribution across the four mutually exclusive 36-week categories also did not differ ($\chi^2(3) = 5.24$, Fisher-Freeman-Halton exact p = 0.189). BPD at 36 weeks PMA occurred in 16.7% of the hydrocortisone group and in none of the dexamethasone group, while death at 36 weeks PMA occurred in 5.6% versus 10.5%. The need for mechanical ventilation at 36 weeks PMA (11.1% versus 5.3%, $\chi^2(1) = 0.42$, Fisher's exact p = 0.604), discharge PMA (36.2 versus 35.1 weeks, t(35) = 1.42, p = 0.166) and duration of hospital stay (34.7 versus 29.1 days, t(35) = 1.39, p = 0.173) were similar. Sensitivity analyses for the four neonates whose 36-week outcome was not ascertained did not alter the absence of a significant difference. In a complete-case analysis the composite occurred in 26.7% versus 11.1% (Fisher's exact p = 0.375), and across best-case and worst-case imputations the p value ranged from 0.062 to 0.693, so the primary result was sensitive to the missing outcomes although no scenario reached statistical significance.

Outcome	Hydrocortisone (n = 18)	Dexamethasone (n = 19)	Test statistic	p-value
Off oxygen support at 36 weeks PMA, n (%)	11 (61.1)	16 (84.2)	$\chi^2(3) = 5.24$	0.189†
BPD (on supplemental oxygen) at 36 weeks PMA, n (%)	3 (16.7)	0 (0.0)	-	-
Death at 36 weeks PMA, n (%)	1 (5.6)	2 (10.5)	-	-
Lost to follow-up at 36 weeks PMA, n (%)	3 (16.7)	1 (5.3)	-	-
Death or BPD at 36 weeks PMA (primary composite outcome), n (%)	4 (22.2)	2 (10.5)	$\chi^2(1) = 0.93$	0.405†
Mechanical ventilation at 36 weeks PMA, n (%)	2 (11.1)	1 (5.3)	$\chi^2(1) = 0.42$	0.604†
Discharge PMA, weeks (mean ± SD)	36.17 ± 1.92	35.08 ± 2.68	$t(35) = 1.42$	0.166
Duration of hospital stay, days (mean ± SD)	34.72 ± 13.39	29.05 ± 11.39	$t(35) = 1.39$	0.173

TABLE 4: Primary and secondary clinical outcomes at 36 weeks postmenstrual age

BPD: bronchopulmonary dysplasia; PMA: postmenstrual age; SD: standard deviation. CI: confidence interval. BPD was defined as the need for supplemental oxygen at 36 weeks PMA. The four 36-week outcome categories (off oxygen, BPD, death and outcome not ascertained) are mutually exclusive and sum to the number of neonates in each group; their distribution was compared as a single 4 × 2 comparison, $\chi^2(3) = 5.24$, and a dash indicates a row included in that comparison. The primary composite of death or BPD was compared as a 2 × 2 table (risk difference 11.7%, 95% CI −12.0% to 35.3%). †Fisher's exact test (Fisher-Freeman-Halton extension for the 4 × 2 comparison), used because at least one expected cell count was below five. The continuous variables were compared using the independent-samples Student t test.

Short-term adverse events were comparable between the groups (Table 5). None of the individual comparisons approached significance: sepsis (50.0% versus 52.6%, $\chi^2(1) = 0.03$, p = 0.873), retinopathy of prematurity (38.9% versus 31.6%, $\chi^2(1) = 0.22$, p = 0.642), ventilator-associated pneumonia (27.8% versus 31.6%, $\chi^2(1) = 0.06$, p = 0.800), intraventricular hemorrhage (22.2% versus 15.8%, $\chi^2(1) = 0.25$, Fisher's exact p = 0.693), necrotizing enterocolitis (16.7% versus 21.1%, $\chi^2(1) = 0.12$, Fisher's exact p = 1.000) and patent ductus arteriosus (16.7% versus 10.5%, $\chi^2(1) = 0.30$, Fisher's exact p = 0.660).

Adverse event	Hydrocortisone (n = 18)	Dexamethasone (n = 19)	Test statistic	p-value
Sepsis, n (%)	9 (50.0)	10 (52.6)	$\chi^2(1) = 0.03$	0.873
Retinopathy of prematurity, n (%)	7 (38.9)	6 (31.6)	$\chi^2(1) = 0.22$	0.642
Ventilator-associated pneumonia, n (%)	5 (27.8)	6 (31.6)	$\chi^2(1) = 0.06$	0.800
Intraventricular hemorrhage, n (%)	4 (22.2)	3 (15.8)	$\chi^2(1) = 0.25$	0.693†
Necrotizing enterocolitis, n (%)	3 (16.7)	4 (21.1)	$\chi^2(1) = 0.12$	1.000†
Patent ductus arteriosus, n (%)	3 (16.7)	2 (10.5)	$\chi^2(1) = 0.30$	0.660†
Bronchopulmonary dysplasia, n (%)	3 (16.7)	0 (0.0)	$\chi^2(1) = 3.45$	0.105†

TABLE 5: Short-term adverse events during the study period

Each adverse event was compared separately between the groups using the Pearson chi-square test; $\chi^2(1)$ is shown beside its p value. Expected cell counts were below five for intraventricular hemorrhage, necrotizing enterocolitis, patent ductus arteriosus and bronchopulmonary dysplasia, so the p values for those four comparisons are from Fisher's exact test (†). No adjustment was made for multiple comparisons.

Discussion

BPD is increasingly understood as the result of an imbalance favoring pro-inflammatory over anti-inflammatory mechanisms in the developing lung, modulated by gestational maturity, the stage at which alveolar development is arrested, birth weight and ventilation strategy [4,13]. Although non-invasive respiratory support has reduced its incidence, a subset of extremely low-birth-weight neonates continue to require ventilation and remain at high risk [1]. Corticosteroids reduce airway inflammation and edema, improve oxygenation and lower ventilatory requirements, which underlies their continued use despite

persisting uncertainty, particularly given the poor neurodevelopmental and respiratory trajectory of survivors with BPD [8,14,15]. In the present cohort of 37 neonates, no statistically significant difference was detected between hydrocortisone and dexamethasone in the primary outcome, in respiratory weaning or in short-term adverse events. This absence of a detected difference is not evidence of equivalence.

The mean maternal age in our cohort (24.3 and 22.8 years in the hydrocortisone and dexamethasone groups, respectively) was lower than in the comparator trials by Onland et al. (median 30 years) and Al-Taweel et al. (29.1 years), plausibly reflecting the younger age at conception and the predominantly rural, lower socioeconomic background of mothers attending our center [16,17]. Cesarean delivery (37.8% overall) and the incidence of pregnancy-induced hypertension (16.2%) were broadly similar to those reports, whereas clinical chorioamnionitis (5.4%) and antenatal steroid coverage (43.2%) were lower, the latter likely reflecting limited antenatal access in this population [16,17].

Neonatal characteristics differed in expected directions. The median gestational age (31 weeks) and mean birth weight (1330 g) were higher than in Onland et al. (25.4 weeks; 775 g) and Al-Taweel et al. (24.9 weeks; 765 g), reflecting the limited survival of the most immature infants in resource-constrained settings [16,17]. Conversely, the proportion small for gestational age (35.1%) was higher, consistent with the contribution of fetal growth restriction, and its associated impairment of pulmonary vascular and alveolar development, to BPD risk in our population [18]. Prenatal inflammation and ventilator- and hyperoxia-induced injury are additional, well-described determinants of lung injury in such infants [19-23].

For the respiratory outcomes, no significant difference was detected. Weaning from oxygen (66.7% versus 73.7%) and downgrading from the entry mode of ventilation (83.3% versus 84.2%) were similar, and a comparable proportion reached room air by the end of therapy. The total duration of ventilation was modestly shorter with dexamethasone (15.8 versus 19.1 days, $p = 0.037$), but this was a nominal finding among several unadjusted comparisons, and it did not translate into a shorter hospital stay (29.1 versus 34.7 days, $p = 0.173$) or a difference in discharge PMA. Mean ventilation and discharge times were considerably shorter than those reported by Al-Taweel et al., again attributable to the greater maturity and birth weight of our cohort [17]. BPD developed in 8.1% of neonates overall, all within the hydrocortisone group, a much lower rate than the 55.2% and 22.2% reported in the comparator studies, in keeping with their more immature populations [16,17].

No significant difference in short-term adverse events was detected. Sepsis affected approximately half of the neonates in each arm, consistent with both comparator studies and attributable to extreme prematurity and prolonged hospitalization predisposing to nosocomial infection [16,17]. The incidence of retinopathy of prematurity (38.9% versus 31.6%) lay between the rates reported by Onland et al. and Al-Taweel et al., while ventilator-associated pneumonia was lower than in the latter, reflecting the shorter ventilation required by our more mature infants [16,17]. Rates of necrotizing enterocolitis, intraventricular hemorrhage and patent ductus arteriosus were within the ranges previously described. Pulmonary hypertension and impaired pulmonary function are important later sequelae of BPD that were beyond the scope of this short-term analysis [24,25]. Corticosteroid use also carries recognized risks such as transient hyperglycemia and adrenal suppression, which were not increased here, although our analysis was not powered for rare events [26-30].

Strengths and limitations

The principal strength of this study is the direct, head-to-head comparison of the two most commonly used corticosteroid regimens in a real-world Indian NICU, an area in which evidence is limited. Its limitations are substantial. First, the sample was small and was not based on a formal power calculation, so only large differences could have been detected; the 95% CI for the primary risk difference (-12.0% to 35.3%) shows that neither equivalence nor non-inferiority can be claimed. Second, the retrospective, single-center design with treatment chosen by the treating neonatologist introduces selection bias and confounding by indication. Although no baseline difference reached statistical significance, antenatal corticosteroid coverage, small-for-gestational-age status, pregnancy-induced hypertension and cesarean delivery were numerically imbalanced, and the small number of primary-outcome events (six) precluded multivariable adjustment for these or other confounders. Third, three neonates died and four left against medical advice, so the 36-week outcome could not be ascertained in the latter four. All 37 were retained in the intention-to-treat analysis, and the sensitivity analyses showed that the primary result depended partly on how these missing outcomes were handled. Fourth, many outcomes were sparse and several secondary comparisons were made without adjustment, so the nominally shorter ventilation with dexamethasone may be a chance finding. Finally, the absence of standardized corticosteroid protocols across settings limits comparability with other studies. The lack of long-term neurodevelopmental follow-up is an important gap, given that this is the central safety concern with postnatal corticosteroids. Larger, prospective, adequately powered randomized trials with long-term follow-up are needed to establish the comparative efficacy and safety of these agents.

Conclusions

This small retrospective study found no statistically significant difference between hydrocortisone and dexamethasone, initiated during the second postnatal week, in death or BPD at 36 weeks PMA, in respiratory

weaning or in short-term adverse events among preterm neonates with evolving lung disease. Equivalence was not shown. Because the study was underpowered and non-randomized, these results cannot establish that the two agents are equivalent or that either is non-inferior to the other.

Until stronger evidence is available, the choice between the two agents in infants who remain oxygen- or ventilator-dependent beyond the first postnatal week will continue to depend on drug availability, cost, institutional experience and the individual infant's comorbidities. These findings are hypothesis-generating. Adequately powered prospective randomized trials with structured long-term neurodevelopmental follow-up are needed before either agent can be preferred over the other in routine practice.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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