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ARTICLE

Hydrocortisone and bronchopulmonary dysplasia: variables associated with response in premature infants

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Abstract

Objective The primary objective was to evaluate hydrocortisone's efficacy for decreasing respiratory support in premature infants with developing bronchopulmonary dysplasia (BPD). Secondary objectives included assessment of the impact of intrauterine growth restriction (IUGR), maternal history of chorioamnionitis, side effects and route of administration associated with hydrocortisone's efficacy. Dexamethasone as second-line treatment to decrease respiratory support was reviewed.

Methods Retrospective chart review of preterm infants requiring respiratory support receiving hydrocortisone.

Results A total of 48 patients were included. Successful extubation was achieved in 50% of intubated patients after hydrocortisone treatment with no major complications. In our small study, history of maternal chorioamnionitis, IUGR or route of administration did not affect the response. Rescue dexamethasone after hydrocortisone therapy was ineffective in the ten patients who failed extubation following hydrocortisone.

Conclusion Hydrocortisone is effective in decreasing respiratory support in patients with developing BPD without major complications. Randomized studies are warranted to confirm our findings.

Introduction

Bronchopulmonary dysplasia (BPD) is a severe complication of prematurity, with a multifactorial pathogenesis including, but not limited to, arrested lung development and persistent inflammation. The definition of BPD has evolved over time most recently defined as oxygen requirement at 36 weeks postmenstrual age (PMA), with grading of severity based on newer modes of noninvasive ventilation [1–4]. Because BPD has been associated with presence of low cortisol levels in premature infants and ongoing inflammation due to mechanical ventilation and oxygen exposure, treatment options include corticosteroids such as hydrocortisone and dexamethasone [5, 6]. However, despite several meta-analyses demonstrating the efficacy of steroid therapy facilitating extubation, concerns surrounding adverse effects, primarily on neurodevelopmental outcome, limited their use [7–9]. Given BPD has proven to be an independent risk factor for poor neurodevelopment, further studies evaluating lower cumulative doses of dexamethasone, administered later in neonatal life, or alternative steroid therapy have been conducted [10]. The DART study (Dexamethasone: A Randomized Trial) compared a lower initial dose of 0.15 mg/kg/day, tapered over 10 days for a cumulative exposure of 0.89 mg/kg versus placebo [10]. This lower cumulative dosing regimen proved to have immediate benefits including a shortened duration of intubation for ventilator-dependent infants; however, the study was not powered to detect

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differences in long-term outcomes. Subsequently, a meta-analysis published in 2008 concluded that there was insufficient evidence to determine an optimal dosing regimen [11]. This has led to the search for alternative treatment, including steroids which target different receptors, such as hydrocortisone. Dexamethasone binds preferentially to the glucocorticoid receptor, promoting neuronal cell apoptosis. In addition to glucocorticoid receptor binding, hydrocortisone also binds to the mineralocorticoid receptor, which is protective against neuronal cell death [12–14]. This dual receptor binding of hydrocortisone and therefore its protective role in neuronal apoptosis is the rationale for hydrocortisone use in our unit (Table 1) [15, 16].

This study aims to evaluate whether hydrocortisone is efficacious and safe as first-line treatment for developing BPD through a reduction in respiratory support requirements. Secondary objectives include assessment of the impact of two prenatal conditions, intrauterine growth restriction (IUGR) and maternal chorioamnionitis (both associated with an increased risk of BPD [17–22]) and route of administration of hydrocortisone on efficacy of decreasing respiratory support. In addition, efficacy of dexamethasone (the DART protocol) [10] was evaluated when administered as second-line therapy if hydrocortisone was believed to be ineffective.

Patients and methods

We conducted a retrospective cohort study consisting of patients who were born at a gestational age (GA) of 32 weeks or less and admitted after birth to our level III Neonatal Intensive Care Unit (NICU) at NYU Winthrop Hospital, in Mineola, New York. Patients were included if they received hydrocortisone 5 mg/kg/day (~50 mg/m^2/day), in three divided doses, for 5 consecutive days to facilitate extubation or to eliminate respiratory support prior to discharge. The cumulative 5 days 25 mg/kg course of hydrocortisone is essentially equivalent to a 0.89 mg/kg cumulative course of dexamethasone. The conversion utilized for this calculation was hydrocortisone 20 mg = dexamethasone 0.75 mg [23]. Patients were included if they were tapered off hydrocortisone for up to 4 additional days. Specifics of taper regimens were at the discretion of the attending neonatologist. Patients were excluded if they were initiated on hydrocortisone for an alternative indication, if they were exposed to an alternative dosing regimen and/or had an incomplete treatment course. Electronic medical records were utilized for data collection.

Table 1 Comparison of hydrocortisone vs dexamethasone, reviewing the different pharmacological properties of the two steroids.

Comparison of hydrocortisone vs dexamethasone		
	Hydrocortisone[a]	Dexamethasone
Duration of action	Short (8–12 h half-life)	Long (36–72 h half-life)
Anti-inflammatory potency	1	25
Equivalent dose	20 mg	0.75 mg
Glucocorticoid effect	Yes	Yes
Mineralocorticoid effect	Yes	No
Albumin bound	Low binding affinity	High binding affinity

[a]Synthetic equivalent of cortisol.

"Actions of synthetic steroids are similar to those of cortisol (hydrocortisone is synthetic cortisol). They bind to the specific intracellular receptor proteins and produce the same effects but have different ratios of glucocorticoid to mineralocorticoid potency." [16]

The primary objective was to evaluate the efficacy of hydrocortisone for the improvement of respiratory status, defined as sustained extubation in intubated patients or effective weaning to room air in the patients on noninvasive ventilation 10 days post treatment completion; based on our clinical experience re-intubation always occurred within a week from the end of the treatment. Hydrocortisone was administered to non-ventilated patients when patients failed multiple attempts to wean to room air, requiring high settings of noninvasive ventilatory support and/or a high oxygen supplementation and were nearing 36 weeks PMA, at the discretion of the attending neonatologist. Secondary efficacy objectives included a decrease in fraction of inspired oxygen requirement (FiO_2) of at least 10%, defined as daily mean FiO_2 the day prior to hydrocortisone initiation (day 0) to the daily mean FiO_2 10 days post treatment initiation. In addition, the combined outcome of a decrease in FiO_2 of at least 10% at 10 days post hydrocortisone, or extubation was reviewed, as well as the changes in the respiratory severity score (RSS) from hydrocortisone day 0 (defined as the day prior to initiation) to day 10 in the intubated patients. RSS, defined as mean airway pressure (MAP) × FiO_2, was utilized instead of oxygenation index, defined as [MAP × FiO_2]/Partial Pressure of Oxygen (PaO_2), as many of our patients did not have an indwelling arterial line for accurate PaO_2 measurement [24]. This index has been used by other authors as a measure of the respiratory status [24, 25].

Secondary objectives included incidence of spontaneous gastrointestinal perforation, patients' growth over a 4-week period, change in head circumference over a 2-month period and any changes identified on head ultrasound as a marker of possible impacted neurodevelopment. A 2-month period was used for head circumference to provide enough time for any slowed growth to be observed. Hyperglycemia and hypertension requiring treatment were reported. Infection was identified via positive cultures (cerebral spinal fluid, blood, and/or urine) during and up to 1 week following

hydrocortisone. In addition, hydrocortisone's efficacy was evaluated to determine if there was a correlation with patient characteristics, such as history of IUGR (based on prenatal ultrasound findings), maternal chorioamnionitis (based on placental pathology diagnosis) or route of administration (intravenous (IV) vs enteral). Patient charts were reviewed for DART protocol administration if hydrocortisone treatment was ineffective and patients remained intubated. Efficacy results for DART were defined as successful extubation by day 10 following treatment and a decrease in the RSS between day 0 and 10.

IV hydrocortisone was supplied as hydrocortisone sodium succinate diluted in normal saline. Hydrocortisone 2 mg/mL oral suspension was utilized for patients who received enteral hydrocortisone. Hydrocortisone tablets were crushed and compounded in a 1:1 ratio of Ora-Sweet and Ora-Plus to create a suspension [26]. Due to the risk of gastrointestinal perforation, hydrocortisone was not administered within 24 h of indomethacin administration [27, 28]. Our hospital's Investigational Review Board approved this study. Consent was not required due to the retrospective nature of the study.

Statistics

Descriptive statistics including mean, median and standard deviation, 25th and 75th percentiles, minimum and maximum values were utilized for continuous measures. Frequency and percentage for categorical measures were calculated for the overall sample, as well as separately for those who did and did not receive DART. The Mann–Whitney test was used to compare subjects who received DART to those who did not for continuous measures. Univariate logistic regression models were utilized to assess patient characteristics and route of administration with respect to the efficacy outcome. Results are reported as odds ratios (OR) with corresponding 95% confidence intervals (CI). The Wilcoxon signed rank test was used to calculate differences in RSS. The average weight gain (g/day), head circumference gain (cm/week), and length gain (cm/week) were calculated separately for each birth weight category. These benchmarks were then used to determine the number of patients who had an appropriate weight gain from initiation to 2 weeks, 2–4 weeks, and initiation to 4 weeks. The paired t test was used to assess the difference in head circumference from initiation to 2 months and was used only if the data were distributed normally. A separate repeated measures analysis of variance with a mixed models approach was used to assess weight and length across time. The repeated (within subjects) factor was time (e.g., 2 weeks prior, 1 week prior, at initiation, 2 weeks post, and 4 weeks post). The Wilcoxon signed rank test was used to calculate the differences in the RSS. A result was considered statistically significant at a p value of <0.05. All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

Results

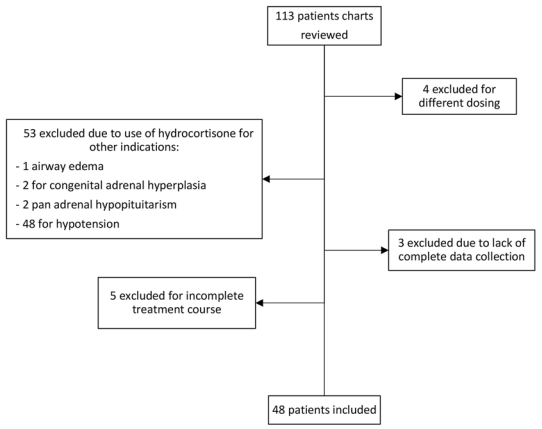
Patient inclusion and characteristics

One hundred and thirteen medical charts of patients in the NICU who received hydrocortisone from January 2007 to October 2017 were reviewed. A total of 48 patients met inclusion criteria, while 65 patients were excluded due to use of hydrocortisone for indications other than decreasing ventilator support for developing BPD, different doses of hydrocortisone being utilized and/or incomplete treatment courses (Fig. 1a). Patient characteristics are reported in Fig. 1b. The median GA of our patient cohort was 25.6 weeks with a median birth weight of 0.76 kg and males accounting for 64.6% of the patients ($n = 31$). Approximately 73% of the patients ($n = 35$) received IV hydrocortisone and 27% ($n = 13$) received the same dose orally. Half of our patients ($n = 24$) were tapered off hydrocortisone and the most commonly utilized taper regimen was a 20% daily decrease (4-day wean, for a total 9-day course). The other half of the cohort received 5 days of hydrocortisone without tapering (Fig. 1b). The majority of patients were administered hydrocortisone between day of life 20–40 and PMA 29–32 weeks (Supplementary Fig. 1a and b) at a median of 33 days with the earliest initiation of hydrocortisone at 9 days.

Efficacy

Extubation was successfully achieved in 50% (20/40) of patients who were intubated at the initiation of hydrocortisone; all of these patients remained extubated up to 10 days post treatment completion. A decrease in FiO_2 by ≥10% at 10 days post hydrocortisone initiation was seen in 52.1% (25/48) of the patients. The combined outcome of FiO_2 decrease of at least 10% at 10 days post hydrocortisone completion or extubation was achieved in 66.7% (32/48) of patients (Fig. 2a). A statistically significant median decrease in the RSS from 3.2 on day 0 of hydrocortisone to 2.7 by day 10 was observed with an overall decrease of -0.7 ($p < 0.0399$) (Fig. 2b). For patients on noninvasive ventilation when they were started on hydrocortisone ($n = 8$), one was completely weaned to room air by day 10 post treatment. Efficacy was not dependent on IUGR status, maternal history of chorioamnionitis, route of hydrocortisone administration, gender, tapering of the dose, GA, day of life at treatment initiation, birth weight and PMA at initiation (Fig. 2c). Based on observed data, the

A



B

Patient's characteristics

Characteristics	n=48* mean ± standard deviation (median)
Gender (male)	31 (64.6%)
Birth weight (kg)	0.77±0.22 (0.76)
Hydrocortisone dosing weight (kg)	1.27±0.58 (1.09)
Gestational age (weeks)	26.1±2.2 (25.6)
DOL at initiation (days)	36.2±21.3 (33.0)
PMA at initiation (weeks)	31.3±4.1 (29.7)
PMA at discharge (weeks)	43.3±4.8 (42.3)
History of PDA	32 (66.7%)
IUGR	9 (18.8%)
Maternal Chorioamnionitis	19 (39.6%)
Antenatal Steroids	38 (80.9%)
Surfactant Survanta® (Beractant) Curosurf® (Poractant-alfa) None	 37 (77.1%) 6 (12.5%) 5 (10.4%)
FiO_2 at initiation (%)	43.8±15.9 (41.5)
Route of administration of hydrocortisone: IV PO	 35 (72.9%) 13 (27.1%)
Hydrocortisone tapered	24 (50.0%)

** Categorical data reported as frequency (%); continuous data presented as mean ± standard deviation (median).*

Fig. 1 Patient flow and patients' characteristics. a Diagram of patient flow. **b** Patient characteristics of the studied population ($n = 48$). DOL: days of life, PMA: postmenstrual age, PDA: patent ductus arteriosus, IUGR: intrauterine growth restriction, IV: intravenous, PO: oral/enteral.

computed powers were 5%, 29%, and 34% for history of IUGR, maternal chorioamnionitis and route of administration, respectively, to detect the differences in response to hydrocortisone: IUGR 4/9 (44%) vs non-IUGR 17/39 (43.6%); maternal chorioamnionitis 6/19 (31.6%) vs non-maternal chorioamnionitis 15/29 (51.7%); route of administration: IV 13/35 (37.1%) vs PO 8/13 (61.5%).

Efficacy outcomes

A

Hydrocortisone n=48	N (%)	95%CI*
Extubation at 10 days post hydrocortisone completion	20/40 (50.0%)	(34.5, 65.5)
FiO_2 decrease ≥ 10% at 10 days post hydrocortisone completion	25/48 (52.1%)	(38.0, 66.2)
FiO_2 decrease ≥ 10% OR extubation at 10 days post hydrocortisone completion	32/48 (66.7%)	(53.3, 80.0)

B

Hydrocortisone n=40	N	Mean	Std Dev	Median	25th Pctl	75th Pctl
Respiratory Severity Score: Day 0	40	4.5	3.1	3.2	2.4	5.6
Respiratory Severity Score: Day 10 (of treatment)	40	4.0	3.3	2.7	2.0	5.2
Difference in Respiratory Severity Score from Day 0 to Day 10	40	-0.5	1.8	-0.7	-1.4	0.4

C

Effect of neonatal characteristics on primary outcome

Effect of infant characteristics and route of administration on primary outcome			OR (95% CI)	p-value #
Sustained extubation* or effective weaning to room air** (total n=48)	IUGR 4 (44.4%)	No IUGR 17 (43.6%)	0.92 (0.61, 1.38)	0.68
	Chorioamnionitis 6 (31.6%)	No Chorioamnionitis 15 (51.7%)	0.81 (0.60, 1.11)	0.19
	IV 13 (37.1%)	PO 8 (61.5%)	0.77 (0.54, 1.08)	0.13
	Male 15 (48.4%)	Female 6 (35.3%)	0.80 (0.58, 1.10)	0.18
	Tapered Dose 12 (50.0%)	No Tapered Dose 9 (37.5%)	1.16 (0.86, 1.58)	0.34
	Gestational Age (for every 7 day increase)		1.58 (0.88, 2.84)[α]	0.13
	DOL at hydrocortisone initiation (for every 7 day increase)		1.03 (0.96, 1.10)[β]	0.45
	Birth Weight (for every 1 kg increase)		1.60 (0.62, 4.16)[γ]	0.33
	PMA at initiation (for every 7 day increase)		1.34 (0.90, 1.99)[δ]	0.15

*Sustained extubation for intubated patients (n=40). Sustained extubation defined as extubation at 10 days post hydrocortisone completion.
**Effective weaning to room air for patients on non-invasive ventilation (n=8)

#Univariate logistic regressions with "Sustained extubation or effective weaning to room air" as the outcome was used for these analyses.

[α] The odds of being extubated or weaned to room air will increase by a factor of 1.58 as an individual's gestational age increases by 7 days.
[β]The odds of being extubated or weaned to room air will increase by a factor of 1.03 as an individual's DOL increases by 7 days.
[γ]The odds of being extubated or weaned to room air will increase by a factor of 1.60 as an individual's birth weight increases by 1 kg.
[δ]The odds of being extubated or weaned to room air will increase by a factor of 1.34 as an individual's PMA at initiation increases by 7 days.

Possible complications

Possible reported complications of postnatal hydrocortisone use are spontaneous gastrointestinal perforation, hyperglycemia, hypertension, and infection [27, 28]. No spontaneous perforations nor episodes of hyperglycemia or hypertension requiring treatment were detected in our cohort (Fig. 3a). An infection rate of 10.4% (5/48) was observed during treatment and within 1 week following completion of hydrocortisone (Fig. 3a). Age did not have a statistically significant impact on infection rate, however, infants who developed an infection were younger and more immature (Fig. 3b).

◀ **Fig. 2 Hydrocortisone efficacy. a** Respiratory outcomes in patients who received hydrocortisone. Extubation was observed in 50% of patients (20/40) who were intubated at initiation. FiO_2 decrease of ≥10% at 10 days post hydrocortisone completion was seen in 52.1% (25/48) of patients. The combined outcome of extubation or decreased FiO_2 by 10% was achieved in 66.7% patients (32/48). Extubation rate was based only on the $n = 40$ subjects who were intubated. **b** Respiratory severity score ($RSS = MAP \times FiO_2$) was calculated at day 0 and day 10 of hydrocortisone treatment. A statistically significant decrease was detected using the Wilcoxon signed rank test in RSS between day 0 of the hydrocortisone treatment and day 10 after the initiation ($p < 0.0399$). Std dev: Standard Deviation. Pctl: Percentile. **c** Efficacy was not affected by intrauterine growth restriction (IUGR) status, maternal history of chorioamnionitis (CAM), route of administration of hydrocortisone, gender, tapering of the dose, gestational age, days of life (DOL) at hydrocortisone initiation, birth weight, postmenstrual age (PMA) at the time of treatment initiation. The primary efficacy outcome was defined as extubation in the 40 patients who were intubated at hydrocortisone initiation or effective weaning to room air in the patients on noninvasive ventilation ($n = 8$) at hydrocortisone initiation. The univariate logistic regression with efficacy for decreased ventilator support as the outcome was used for these analyses.

Patient weight increased daily by a median of 16.57 g in the first 2 weeks after initiation of therapy and by 22.75 g in the following 2 weeks after treatment (Supplementary Fig. 2a) with an overall steady increase from the time before and after hydrocortisone treatment ($p = 0.003$). Patient length increased by a median of 1.05 cm per week in the first 2 weeks following initiation of therapy and by 1.5 cm per week in weeks 2–4 following initiation (Supplementary Fig. 2b). Based on data published by Anchieta et al., this is a normal weight and length growth rate for a premature baby [29]. Lastly, we reviewed head circumference growth and head ultrasound results after hydrocortisone treatment as an indication for potential future neurodevelopmental impairment. For all patients, head circumference increased, as expected [29], by a median of 1 cm weekly up to 2 months post treatment (Fig. 3c and Supplementary Fig. 2c). Head ultrasound results worsened during and soon after hydrocortisone therapy in two patients. One patient presented with findings consistent with periventricular leukomalacia (PVL) during treatment, suggestive of complicated birth and perinatal history as a possible cause. The second patient developed grade 1 intraventricular hemorrhage (IVH) during hydrocortisone treatment with progression to PVL one month later. In this case, we cannot exclude any association between hydrocortisone and the head ultrasound findings. Both of these patients did not receive DART therapy during their NICU admission.

Use of DART protocol

Anecdotally in our unit our clinical team was more likely to follow-up with dexamethasone administration if patients did not show improvement in their respiratory status following hydrocortisone treatment. Dexamethasone was dosed according to the DART protocol [10] and was administered to 50% (10/20) of our patients after hydrocortisone was unsuccessful in leading to extubation. Of those who were administered dexamethasone, 20% (2/10) were extubated during the DART course (Fig. 4a), however, both patients were reintubated by 10 days posttreatment completion. There was not a significant decrease in the median RSS from day 0 at 13.2 to 6.4 at day 10 in the DART group, $p < 0.2754$ (Fig. 4b) Patients who later received DART therapy (hydrocortisone non-responders, HC-NR) were younger at the time of hydrocortisone initiation compared with the cohort who did not receive DART therapy, with a median day of life of 25 and PMA of 29.7 weeks. (Fig. 4c). Most patients were ~40–60 days of life at time of DART initiation and the majority of patients were initiated on DART within 2 weeks of hydrocortisone treatment (Supplementary Fig. 3). These data suggest that dexamethasone, after hydrocortisone treatment, was not effective in our patient population.

Discussion

Our findings suggest that hydrocortisone therapy at 5 mg/kg/day administered for 5 consecutive days significantly decreases respiratory support, improves the RSS and increases the chance of extubation in preterm infants older than 10 days at risk for BPD.

The dose of 5 mg/kg/day used in this study is considered a high hydrocortisone dose, however, it was previously used in earlier studies. The authors of these studies concluded that hydrocortisone did not negatively impact neurodevelopment, was effective in increasing the chance of extubation and decreased BPD [30, 31]. Similar to our study, other reports have observed a positive impact of hydrocortisone on ventilator-dependent infants, with the lack of negative effect in the neurodevelopmental outcome when started later in neonatal life [8, 31].

We focus our attention on two different, but very common, subsets of patients in the NICU including infants born with a prenatal diagnosis of IUGR and infants born to mothers affected by chorioamnionitis. IUGR infants are known to have a persistent increased level of serum cortisol due to a chronic stress condition in utero [32]. Therefore, we did not expect hydrocortisone to improve IUGR infants' respiratory status due to their prolonged exposure to endogenous cortisol levels and subsequent resistance to steroids. Vice versa, maternal chorioamnionitis acutely exposes the fetus to inflammatory mediators leading to a potentially increased risk for BPD [21, 22, 33]. Therefore, we hypothesized that steroid treatment would have helped to

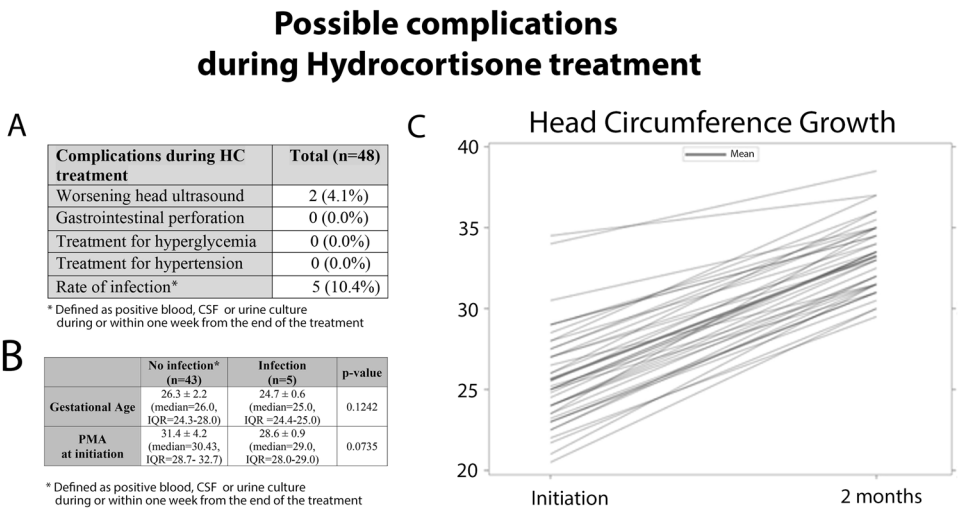


Fig. 3 Hydrocortisone and safety outcomes. a Complication rate in the studied population ($n = 48$). **b** Younger patients, based on both gestational age and PMA, had a trend of an increased risk of infection compared with older infants. Infection was identified based on positive cultures during and up to 1 week after the end of hydrocortisone treatment. The Mann–Whitney test, the non-parametric counterpart to the two-sample *t*-test, was used to compare those subjects with and without infection for gestational age and PMA at initiation of hydrocortisone. IQR: Interquartile range. **c** Head circumference is depicted as the mean growth from initiation of hydrocortisone to 2 months after therapy.

decrease the ongoing inflammation and consequently improve respiratory status in infants of mothers with a history of maternal chorioamnionitis. In addition, our hypothesis was based on a study that reported hydrocortisone increased survival without BPD, in infants exposed to histological chorioamnionitis [28]. Although our study was not powered to detect a statistical association, our data suggest a lack of association regarding the response to hydrocortisone and these two prenatal conditions. It is possible that the delayed use of steroids decreased the chance of any prenatal conditions to impact hydrocortisone response.

We reviewed the possible collateral effects of hydrocortisone treatment in premature infants. In general, steroids with a glucocorticoid effect are considered catabolic yielding growth suppression [34]. Our patients did not experience impaired growth in terms of length and head circumference. Furthermore, there was a steady increase in weight. Post-hoc pairwise comparison showed a non-significant decrease in the rate of weight gain during the first 2 weeks following initiation of hydrocortisone ($p = 0.522$), but a significant increase was observed 2 weeks later ($p = 0.003$). These data suggest the importance of optimizing nutrition during and after hydrocortisone treatment. Consistent with other retrospective reports where hydrocortisone was used after the first week of life, we did not detect any effect on head circumference growth as a predictor of brain development and neurodevelopmental outcome [31, 35–42].

Infection throughout hydrocortisone treatment and 1 week thereafter was documented in 10.4% (5/48) of patients, consistent with our overall NICU infection rate in a similar patient population (10.3%) based on our NICU Vermont Oxford Network data. We observed a trend toward a higher likelihood of infection in the younger and more immature patients, similar to other reports [43].

Bioavailability of oral hydrocortisone is on average 96% in adult patients [44], indicating almost complete absorption, but in preterm infants the bioavailability extent remains unknown. Given the scarcity of this data in preterm infants, we wanted to assess if oral hydrocortisone was as effective as an IV route of administration. Despite our study not being powered to show a statistically significant difference, we observed that route of administration had no impact on drug efficacy. Oral treatment should be considered when managing patients' who do not require IV lines.

We utilized essentially equivalent doses of hydrocortisone and dexamethasone used in the DART protocol [23]; however, because of the variances in their receptor binding, we hypothesized that dexamethasone will be an effective rescue therapy if patients failed to be extubated following hydrocortisone treatment. The use of DART was based on attending's clinical discretion ($n = 10$). Out of the patients who received DART, two were extubated, however were reintubated shortly thereafter. Furthermore, the median RSS did not show a statistically significant decrease, confirming the lack of efficacy of dexamethasone treatment. The rate of extubation in our population following hydrocortisone treatment was close to the rate reported in the DART study [10] (50% vs 60%) suggesting that hydrocortisone can be used as first-line

Rescue DART efficacy outcome

A

DART n=10	N (%)	95% CI*
Extubation	2 (20%)	(2.5, 55.6)

B

DART n=10	N	Mean	Std Dev	Median	25th Pctl	75th Pctl
Respiratory Severity Score: Day 0	10	10.5	6.67	13.2	3.7	16.6
Respiratory Severity Score: Day 10 (of treatment)	10	7.9	6.6	6.4	3	10.8
Difference in Respiratory Severity Score from Day 0 to Day 10	10	-2.6	5	-1.4	-6.1	0.4

C

Variable	NO DART (n=38)	HC-NR DART (n=10)	p-value
DOL (days)	38.6 ± 22.8 (median=34.0, IQR=21.0-44.0)	26.8 ± 9.8 (median=25.0, IQR=21.0-36.0)	0.222
Birth Weight (kg)	0.8 ± 0.2 (median=0.8, IQR=0.6-0.8)	0.7 ± 0.2 (median=0.7, IQR=0.6-0.8)	0.381
Gestational Age (weeks)	26.0 ± 2.2 (median=25.4, IQR=24.1-27.0)	26.5 ± 1.9 (median=26.0, IQR=25.1-28.7)	0.264
PMA at initiation (weeks)	31.3 ± 4.4 (median=29.9, IQR=28.6-32.7)	30.4 ± 2.2 (median=29.7, IQR=29.1-31.1)	1.000
PMA at discharge (weeks)	42.5 ± 4.2 (median=41.9, IQR=40.6-44.7)	46.1 ± 6.0 (median=46.4, IQR=42.3-49.3)	0.071

Fig. 4 Dexamethasone (DART) efficacy and patient characteristics. **a** Extubation was observed in 2 out of 10 patients who received DART after hydrocortisone treatment. However, both of the infants were reintubated within 10 days. **b** Respiratory severity score (RSS = MAP × FiO_2) was calculated at day 0 and day 10 of dexamethasone treatment. There was not a significant decrease in the median RSS from day 0 to day 10 in the DART group. Wilcoxon signed rank test in RSS between day 0 of the DART treatment and day 10 after the initiation ($p < 0.2754$). Std Dev: standard deviation. Pctl: percentile. **c** Dexamethasone was administered via the DART protocol to 50% (10/20) after failure to respond to hydrocortisone. Patients who later received DART compared with infants who responded to hydrocortisone and therefore did not receive DART (NO DART) were younger at time of hydrocortisone administration, with a median of 25 days of life and PMA at initiation of hydrocortisone of 29.7 weeks. The Mann–Whitney test, the non-parametric counterpart to the two-sample *t*-test, was used to compare those who received DART to those who did not receive DART. HC-NR: Hydrocortisone non-responder. IQR: Interquartile range.

treatment for BPD. The delayed administration of DART may be a contributing factor for the suboptimal response observed, as previously discussed by Cuna et al. [45]. Furthermore, a previous study reported a lack of clear benefit of multiple courses of oral steroids to wean off supplemental oxygen in patients affected by BPD [46]. Due to the multifactorial pathogenesis of BPD, it is possible that a subpopulation of infants will not respond to steroids. Future studies would help to address this question.

Limitations

Although this study showed strength in its assessment of the use of hydrocortisone in patients with developing BPD, it also had several limitations. The limitations include the lack of a control group due to the retrospective nature of the study, being a single center study and the small sample size. The number of patients included in the study was based on feasibility and availability of resources, therefore a formal sample size calculation was not possible to perform. The patients' included in the study were born with a median GA of 25 weeks and a birth weight less than 1 kg providing clinically useful information on the subgroup of patients at higher risk for BPD. A prospective double-blinded study would need to be performed to clarify which corticosteroids should be used as a safer first- or second-line treatment in preterm ventilated infants. Finally, head circumference changes were followed for only 2 months following treatment and even though it has been proven to be a tool to identify neonates at risk for neurodevelopmental disorders, it does not directly correlate with neurodevelopmental outcome [39]. Bearing in mind the above considerations, the results of our study still provide useful information on the use of hydrocortisone in premature infants with developing BPD as a first-line steroid treatment to decrease ventilator support.

Conclusion

In conclusion, hydrocortisone 5 mg/kg/day for 5 days increased the chance of extubation or decreased respiratory support and RSS in infants with developing BPD without major side effects. With the caveat of this being a small and underpowered study for these variables, maternal history of chorioamnionitis, IUGR status, and route of administration did not affect odds of response. However, this might be related to the lack of statistical power addressing these variables in our study. In addition, dexamethasone administration after hydrocortisone in our population was not successful.

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Author contributions CC and CT designed the research study, analyzed the data and wrote the paper. CC, CT, ST, IK, and VT acquired the data. MA performed statistical analysis. NH reviewed the final paper.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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