HHS Public Access

Author manuscript

J Perinatol. Author manuscript; available in PMC 2021 August 15.

Published in final edited form as:

J Perinatol. 2021 April ; 41(4): 794–800. doi:10.1038/s41372-021-00943-9.

The Use of Supplemental Hydrocortisone in the Management of Persistent Pulmonary Hypertension of the Newborn

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Abstract

Objective: Characterize association between hydrocortisone receipt and hospital outcomes of infants with persistent pulmonary hypertension of the newborn (PPHN).

Study design: Cohort study of infants ≥34 weeks with PPHN who received inhaled nitric oxide at <7 days of age (2010–2016). We generated propensity scores, and performed inverse probability weighted regression to estimate hydrocortisone effect on outcomes: death, chronic lung disease (CLD), oxygen at discharge.

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Dr. Aleem is the guarantor who accepts full responsibility for the work and conduct of the study, and had access to the data. Dr. Aleem conceptualized and designed the study, and contributed to the data interpretation, the drafting of the initial manuscript, and reviewing and revising the manuscript.

Mr. Robbins contributed to the data interpretation and the manuscript drafting.

Ms. Murphy contributed to the data interpretation and the manuscript drafting.

Mr. Elliott contributed to the data interpretation and the manuscript drafting.

Ms. Akinyemi contributed to the data interpretation and the manuscript drafting.

Mr. Paredes contributed to the data interpretation and the manuscript drafting.

Dr. Benjamin contributed to the study design, data analyses, and the critical revision of the manuscript for important intellectual content.

Dr. Tolia contributed to the data interpretation and the critical revision of the manuscript for important intellectual content.

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Dr. Goldberg contributed to the data interpretation and the critical revision of the manuscript for important intellectual content.

Dr. Greenberg contributed to the conception and design of the study, supervised the drafting of the manuscript, interpreted the data analyses, and reviewed and revised the manuscript. Dr. Greenberg had full access to all the data and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict of Interest: RGG has received support from industry for research services (https://dcri.org/about-us/conflict-of-interest/). The other authors have no conflicts of interest relevant to this article to disclose.

Results: Of 2743 infants, 30% received hydrocortisone, which was associated with exposure to mechanical ventilation, sedatives, paralytics, or vasopressors ($p<0.001$). There was no difference in death, CLD, or oxygen at discharge. In infants with meconium aspiration syndrome, hydrocortisone was associated with decreased oxygen at discharge (odds ratio 0.56; 95% confidence interval 0.21, 0.91).

Conclusions: There was no association between hydrocortisone receipt and death, CLD, or oxygen at discharge in our cohort. Prospective studies are needed to evaluate the effectiveness of hydrocortisone in infants with PPHN.

Introduction

Persistent pulmonary hypertension of the newborn (PPHN) is a syndrome characterized by hypoxemia and elevated pulmonary vascular resistance secondary to failure of circulatory adaptation in the immediate postnatal period [1]. The prevalence of PPHN has been reported to be 1.9 per 1000 live births with a wide variability across centers, ranging from 0.4–6.8 per 1000 live births [2]. Overall mortality of PPHN in infants participating in randomized controlled trials ranged from 7–15% [3–5]. In surviving infants, 24% of infants are diagnosed with chronic lung disease (CLD), and nearly 16% of infants with PPHN are discharged home on oxygen.

Inhaled nitric oxide (iNO) is the only United States Food and Drug Administration-approved agent for the management of PPHN. Even though iNO improves oxygenation and reduces the use of extracorporeal membrane oxygenation, the overall response is modest [6]. A meta-analysis of 17 randomized controlled trials noted that nearly one-third to half of infants, particularly those with moderate disease severity, demonstrated a limited response to iNO, with no effect on survival rates [6]. Therefore, alternative agents are currently being used in clinical practice, and include pulmonary vasodilators, such as sildenafil, milrinone, and bosentan [7–9]. Importantly, none of these agents are currently United States Food and Drug Administration-approved for use in the neonatal population. The unsatisfactory clinical response to iNO seen in some infants speaks to the need for new therapies for the management of PPHN to augment current therapeutic strategies, and to prevent long-term complications of standard management.

Due to its potential physiologic effects, hydrocortisone is one such drug of interest. In normal pulmonary vasculature, local production of nitric oxide (NO) leads to production of cyclic guanosine monophosphate (cGMP), which is a vital second messenger for vasorelaxation [10]. In the lungs, cGMP is in turn inactivated by phosphodiesterase-5 (PDE5), which is the primary phosphodiesterase in lung vasculature [10]. At birth, there is an increase in NO levels, and a decrease in PDE5 activity with a corresponding increase in cGMP levels, leading to increased vasodilatory response in the pulmonary vasculature [10]. Disruption of the NO-cGMP signaling pathway plays a critical role in the persistence of elevated pulmonary vascular pressures, and the pathogenesis of PPHN [10]. There is emerging evidence from neonatal lamb studies that suggests exposure to even brief periods of hyperoxia can increase pulmonary vascular contractility [11, 12]. In the neonatal lamb model of PPHN, administration of hydrocortisone improved oxygenation by decreasing

PDE5 expression and activity, and increasing cGMP [13, 14]. Hydrocortisone also reduced lung injury caused by oxidative stress by reducing levels of reactive oxygen species [13, 14]. Moreover, genetic studies have revealed an association between variants in the cortisol pathway and PPHN [15]. The variations in the Corticotropin Releasing Hormone Receptor 1 gene and Corticotropin Releasing Hormone Binding Protein gene that have been documented in infants with PPHN may lead to decreased cortisol levels in these infants [15]. These data suggest that hydrocortisone therapy may have a role in the management of PPHN. The objective of this study was to characterize the association between hydrocortisone use and hospital outcomes in infants being treated with iNO for PPHN.

Methods

Study design and setting

We conducted a retrospective cohort study using a clinical database of hospitalized infants from neonatal intensive care units (NICU) managed by the Pediatrix Medical Group, who were discharged or died between 2010 and 2016. We included infants if they were ≥34 weeks gestational age, were diagnosed with PPHN, congenital diaphragmatic hernia (CDH), or meconium aspiration syndrome (MAS) at <7 days of age, and received iNO at <7 days of age. We excluded infants if they received hydrocortisone after iNO was weaned off, or if they had a major congenital anomaly, except CDH.

De-identified data, including demographic, clinical, and maternal data, was obtained from the Pediatrix BabySteps Clinical Data Warehouse, which is an electronic medical record database that prospectively captures information from daily progress notes and other documentation generated by physicians using a computer-assisted tool [16]. This study was approved by the Duke University Institutional Review Board as exempt research.

Definitions

Our primary outcomes of interest were a composite outcome of death prior to discharge and CLD, and the use of oxygen at discharge. We defined the use of oxygen at discharge as receipt of supplementary oxygen on the day of or the day before discharge. This outcome was not evaluated for infants who were not discharged home. CLD was defined as the receipt of supplemental oxygen or respiratory support (nasal cannula, continuous positive airway pressure, or mechanical ventilation) continuously from a postnatal age of 28 to 34 days [17]. We defined PPHN, CDH, and MAS by clinician diagnosis in the electronic medical record. We determined small for gestational age status using the Olsen definition [18]. Treatment with iNO was determined as use of iNO for any duration. We defined treatment with hydrocortisone as any exposure to intravenous or enteral hydrocortisone while on iNO. Since hydrocortisone is very bioavailable and the indication for use is unavailable from the dataset, we chose to include both forms in the analyses. We defined the use of vasopressors as receipt of dopamine, dobutamine, epinephrine, vasopressin, milrinone, or norepinephrine while on iNO, and the use of sedative or paralytics as the receipt of opioids, benzodiazepines, paralytics or other drugs (chloral hydrate, dexmedetomidine, ketamine, chlorpromazine) while on iNO. We defined early-onset sepsis as a positive culture (blood, urine obtained by suprapubic tap or in-and-out catheterization,

or cerebrospinal fluid) occurring within the first 7 days of age. The use of hydrocortisone and other drug therapies, as well as the decision to use oxygen at discharge, was at the discretion of the treating clinician.

Statistical analyses

Infants were divided into 2 groups: those who received hydrocortisone and those who did not. We compared demographics and clinical characteristics between the 2 groups using the Wilcoxon rank-sum test for continuous variables and the chi-squared test for categorical variables. We evaluated the percentage of infants receiving hydrocortisone over time by discharge year.

Since exposure to hydrocortisone is likely to be associated with severity of illness, we used propensity scores to obtain similar populations for comparison. We included the following variables in a logistic regression model to generate propensity scores: gestational age, sex, race/ethnicity, small for gestational age status, exposure to prenatal steroids, prolonged rupture of membranes (PROM) >18 hours, Apgar score at 5 minutes, surfactant exposure, form of ventilation when iNO started (non-invasive, conventional mechanical ventilation, or high frequency ventilation), age at the time of first intubation, diagnosis of early-onset sepsis, use of vasopressors while on iNO, use of sedatives or paralytics while on iNO, use of dexamethasone while on iNO, use of antibiotics while on iNO, use of extracorporeal membrane oxygenation, site, and discharge year. The first and second moments of the covariates were well balanced between the treated and untreated groups, and a chi-square test failed to reject the null of balance [19].

We then used the propensity scores to perform inverse probability-weighted regression adjustment to estimate the average effect of receipt of hydrocortisone on each of the outcomes of interest: diagnosis of CLD, oxygen use at discharge, death before discharge, and a composite outcome of death and CLD. We reported odds ratios (OR) and 95% confidence intervals (CI) of the effect of hydrocortisone exposure on each outcome. In order to assess the effect of hydrocortisone on idiopathic PPHN, as a pre-specified secondary analysis, we excluded infants with CDH or MAS and evaluated whether there were major changes to the results. We chose to exclude infants with CDH for the secondary analysis, since these infants may have PPHN secondary to structural remodeling of the pulmonary vasculature during fetal development [20]. Similarly, we chose to exclude infants with MAS for the secondary analysis, since their disease process may be related to parenchymal lung disease [21]. Subgroup analyses were also performed on infants with a diagnosis of MAS. All analyses were performed using Stata version 16.1 (StataCorp LLC, College Station, Texas); p-values <0.05 were considered significant.

Results

A total of 2743 infants from 164 NICUs met the inclusion criteria, with a median (25^{th}–75^{th} percentiles) gestational age of 38 weeks (37–40) and birth weight of 3280 g (2890–3711 g). Overall, 810/2743 (30%) infants were exposed to hydrocortisone in the first 7 days of age. A majority of infants (781/810) received intravenous hydrocortisone only, 22/810 received enteral hydrocortisone only, and 7/810 received both intravenous and enteral hydrocortisone.

The percentage of infants who received hydrocortisone remained stable during the study period (Figure 1).

Infants exposed to hydrocortisone were more likely to be of black race ($p<0.001$); have lower Apgar scores at 5 minutes ($p=0.02$); receive surfactant ($p=0.001$); and be exposed to sedatives or paralytics ($p<0.001$), vasopressors ($p<0.001$), and antibiotics ($p<0.001$; Table 1). Infants who received hydrocortisone were also more likely to be on high-frequency ventilation when iNO was initiated ($p<0.001$), and be treated with extracorporeal membrane oxygenation ($p<0.001$; Table 1).

Overall, 182/2221 (8%) of infants died and 167/2186 (8%) had CLD. A total of 1980/2743 (72%) infants were discharged home, and 187/1975 (9%) infants discharged home received oxygen at discharge. Oxygen status was unknown for 5 infants who were discharged home. On unadjusted analyses, infants exposed to hydrocortisone had a statistically significant lower frequency of CLD ($p<0.001$; Table 2), but there was no difference in death or receipt of oxygen at discharge between groups. On adjusted analysis, the use of hydrocortisone in conjunction with iNO had no association with death, CLD, oxygen supplementation at discharge, or the composite outcome of death prior to discharge or CLD in the full cohort (Table 3). The results remained the same after exclusion of infants with CDH and MAS. Because of transfer of infants to a different service (40/2743) or hospital (540/2743), we had some missing data for the outcomes of interest.

We performed a subgroup analyses on infants with a diagnosis of MAS. Our cohort included a total of 892 infants with MAS, of whom 288 (32%) received hydrocortisone. Among infants with MAS, 40/702 (6%) of infants died and 67/679 (10%) had CLD. A total of 633/892 (71%) infants with MAS were discharged home, 77/632 (12%) infants received oxygen at discharge, and 1 infant had an unknown status of oxygen at discharge. On adjusted analysis, hydrocortisone exposure was significantly associated with decreased oxygen supplementation at discharge (OR 0.56, 95% CI 0.21, 0.91; $p=0.002$). Exposure to hydrocortisone was not associated with death, or the composite outcome of death or CLD in this subgroup (Table 3). Since only 67 infants with MAS had CLD, we were unable to analyze the effect of hydrocortisone exposure on CLD in this group. Similarly, we were also unable to analyze the effect of hydrocortisone exposure on the outcomes of interest in infants with CDH because there were only 32 infants with CDH in the cohort.

Discussion

To our knowledge, this is the largest study evaluating the effects of hydrocortisone on hospital outcomes in term and late preterm infants displaying PPHN physiology, including CDH. After adjusting for markers of clinical severity in our cohort of 2743 infants with PPHN, hydrocortisone exposure did not translate to lower odds of death, CLD, or use of oxygen at discharge. Hydrocortisone was used more commonly than we expected; 30% of infants with PPHN treated with iNO were also treated with hydrocortisone. In our unadjusted cohort, infants treated with hydrocortisone had a more severe clinical course, as indicated by higher vasopressor, sedatives, and paralytics use, as well as high-frequency ventilation support in the group. This is not surprising because hydrocortisone is used as

rescue therapy prior to extracorporeal membrane oxygenation deployment in some centers [22]. We were able to achieve balance between the groups using inverse probably-weighted regression adjustment.

The main hallmark of PPHN is sustained pulmonary vascular pressures elevated to suprasystemic levels, leading to increased cardiac right-to-left shunting, with resultant severe systemic hypoxemia [23]. Evidence from human studies demonstrates that hydrocortisone use leads to increased blood pressure and hemodynamic stability in critically ill infants, and those with vasopressor-resistant hypotension [24–26]. Stabilization and increase in systemic blood pressure decreases the right-to-left cardiac shunting, thereby improving oxygenation in infants with PPHN [23]. Another proposed mechanism of hydrocortisone's beneficial role in the management of PPHN is through its effect in reducing pulmonary vasoconstriction and inflammation, as seen in animal models. In a neonatal lamb model of PPHN induced by ductal ligation, hydrocortisone has been shown to improve oxygenation by promoting smooth muscle relaxation, and reducing damage caused by oxidative stress [13, 14]. These findings make hydrocortisone an attractive agent for use in the management of PPHN.

In a recently published retrospective study, 15 infants with severe PPHN who received iNO were evaluated [26]. These infants were also treated with dopamine for inotropic support prior to hydrocortisone administration. A significant improvement in systolic blood pressure, PaO2/FiO2 ratio, as well as a decrease in inotropic score, and oxygenation index were observed after the administration of hydrocortisone. The improvement in systolic blood pressure persisted even after discontinuation of hydrocortisone. While our findings are suggestive against the use of hydrocortisone in conjunction with iNO in late preterm and term infants, our outcome measures were notably different, and given the limitations of our database, we were unable to evaluate effects on blood pressure and oxygenation.

On subgroup analyses of infants with MAS, we found a small, but statistically significant decrease in the odds of oxygen use at discharge associated with hydrocortisone use. This finding is consistent with prior small studies, which have shown that glucocorticoid therapy is beneficial in infants with MAS by significantly decreasing oxygen dependency and duration of hospitalization, without a significant increase in the incidence of infections [27, 28]. These findings are likely related to the anti-inflammatory properties of glucocorticoids, leading to a reduction in pulmonary edema and pulmonary vasoconstriction [29]. This mechanism is further supported by animal studies. In a porcine model of meconium aspiration-induced pulmonary hypertension, methylprednisolone pretreatment was associated with improved oxygenation and attenuation of the pulmonary-hypertensive response by prevention of pulmonary postarterial resistance [30]. Consequently, the use of hydrocortisone, particularly in cases of severe PPHN secondary to MAS, may be warranted; however, further prospective studies are needed to demonstrate safety and efficacy.

Our study was strengthened by the use of data from the Pediatrix Clinical Data Warehouse, which allowed us to identify a large and contemporary diverse study sample. Our cohort included infants from 164 community and academic NICUs across the United States. However, our study has several limitations related to the retrospective observational design. Infants with more severe illness are more likely to be prescribed hydrocortisone; as a result,

the clinical illness severity presents an important confounding variable that is difficult to account for using an observational dataset. Measures of hypoxic respiratory failure severity, such as alveolar-arterial gradient or oxygenation index, were not available from the dataset. In order to adjust for illness severity, we used propensity scores to perform inverse probability-weighted regression adjustment for our analysis. We used factors that we assumed to be markers of illness severity (and, therefore, associated with hydrocortisone exposure) to generate propensity scores. Despite this, it is likely that there were residual confounding factors that we were unable to control for, such as vital signs, results from imaging studies, etc. Data on medication dosage and threshold for pharmacotherapy initiation was unavailable from the database, so we were unable to assess how these factors influenced clinical outcomes. Finally, we were unable to account for physician skill level, practice variation across centers, or other measures of quality that may affect likelihood of hydrocortisone exposure.

Conclusions

In conclusion, in this large cohort study, we found that hydrocortisone use is not associated with improved survival, lower oxygen use at discharge, or lower rates of CLD in the overall cohort of infants with PPHN. Yet despite these findings, hydrocortisone is used in nearly 30% of cases of PPHN in NICUs across the United States. In infants with MAS, hydrocortisone use was associated with a decreased need of oxygen use at discharge. The findings from our study have important implications for understanding the efficacy of hydrocortisone use in this population, and can be used as a basis for future trial development. A randomized controlled trial or prospective cohort studies accounting for illness severity is needed to examine the effectiveness and safety of hydrocortisone use in the management of PPHN.

Acknowledgments

Sources of funding: This work was supported by Duke Clinical Research Institute's R25 Summer Training in Academic Research (STAR) Program (grant #5R25HD076475-07).

This work was partially funded under the National Institute of Child Health and Human Development (NICHD) contract (HHSN275201000003I) for the Pediatric Trials Network (PI Danny Benjamin). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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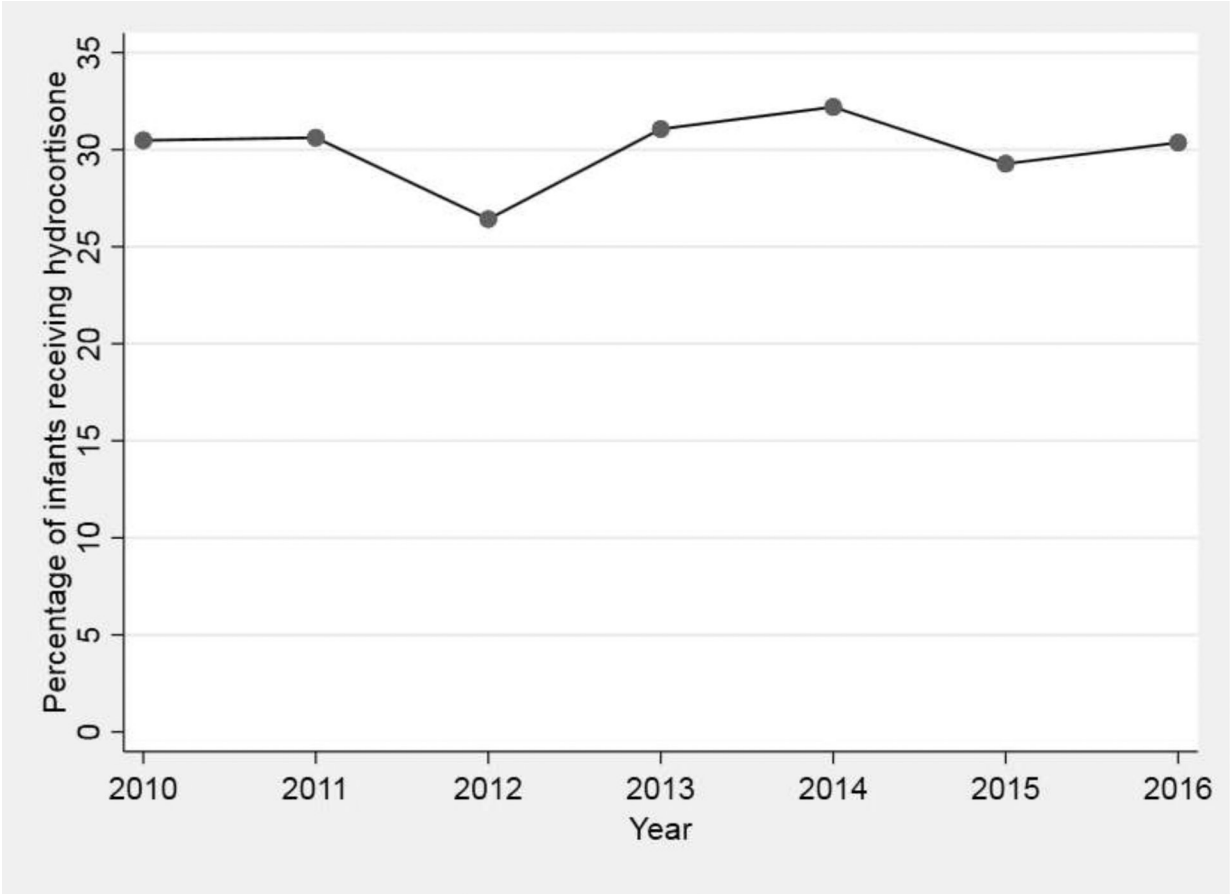

Figure 1.

Percentage of infants with PPHN receiving hydrocortisone, by year.

PPHN, persistent pulmonary hypertension of the newborn

Table 1.

Demographics and clinical characteristics

Covariates used in estimation of propensity scores	Hydrocortisone + iNO (N=810)	iNO alone (N=1933)	p-value
Gestational age, weeks, n (%)			0.37
34–36	162 (20)	390 (20)	
37–38	230 (28)	605 (31)	
39–40	331 (41)	757 (39)	
>40	87 (11)	181 (9)	
Male, n (%)	492 (61)	1119 (58)	0.17
Race/ethnicity, n (%)			<0.001
White	362 (47)	995 (54)	
Black	126 (16)	377 (21)	
Hispanic	220 (29)	344 (19)	
Other	62 (8)	115 (6)	
Birth weight, grams, n (%)			0.40
<2500	66 (8)	179 (9)	
2500–3499	432 (53)	1057 (55)	
>3500	311 (38)	697 (36)	
Small for gestational age, n (%)	57 (7)	141 (7)	0.85
Exposed to prenatal steroids, n (%)	28 (3)	85 (4)	0.26
Prolonged rupture of membranes, n (%)	38 (5)	81 (4)	0.54
Apgar score at 5 minutes, n (%)			0.02
0–3	125 (16)	244 (13)	
4–6	196 (25)	412 (22)	
7–10	469 (59)	1210 (65)	
Ventilation type when iNO started, n (%)			<0.001
Non-invasive ventilation	39 (5)	271 (14)	
Conventional mechanical ventilation	252 (31)	872 (45)	
High frequency ventilation	519 (64)	782 (41)	
Received surfactant, n (%)	515 (64)	1095 (57)	0.001
Antibiotics while on iNO, n (%)	784 (97)	1768 (91)	<0.001
Vasopressors while on iNO, n (%)	744 (92)	1105 (57)	<0.001
ECMO, n (%)	67 (8)	61 (3)	<0.001
Sedatives/paralytics while on iNO, n (%)	773 (95)	1551 (80)	<0.001
Received dexamethasone while on iNO, n (%)	52 (6)	95 (5)	0.11
Early-onset sepsis, n (%)	31 (4)	48 (2)	0.06

iNO, inhaled nitric oxide; ECMO, extracorporeal membrane oxygenation

Table 2.

Unadjusted comparisons of outcomes of interest

Outcomes of interest	Hydrocortisone + iNO (N=810)	iNO alone (N=1933)	p-value
Overall			
Death or CLD, n (%)	141 (21)	199 (14)	<0.001
Death, n (%)	64 (9)	118 (8)	0.25
CLD, n (%)	82 (12)	85 (6)	<0.001
Oxygen at discharge, n (%)	56 (9)	131 (10)	0.75
MAS subgroup			
Death, n (%)	14 (6)	26 (6)	0.90
CLD, n (%)	36 (14)	31 (7)	0.004
Oxygen at discharge, n (%)	22 (10)	55 (14)	0.15

CLD, chronic lung disease; iNO, inhaled nitric oxide; MAS, meconium aspiration syndrome

Table 3.

Estimated average effect of hydrocortisone exposure on outcomes after inverse probability weighted regression adjustment

	OR (95% CI)	p-value
Full cohort		
Death or CLD	1.00 (0.74, 1.26)	0.99
Death prior to discharge	0.86 (0.57, 1.16)	0.36
CLD	1.27 (0.82, 1.72)	0.24
Oxygen at discharge	0.79 (0.49, 1.09)	0.17
MAS subgroup		
Death or CLD	1.11 (0.54, 1.69)	0.70
Death prior to discharge	0.98 (0.20, 1.75)	0.95
Oxygen at discharge	0.56 (0.21, 0.91)	0.01

CI, confidence interval; CLD, chronic lusng disease; MAS, meconium aspiration syndrome; OR, odds ratio