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A Randomized Controlled Study of Low-Dose Hydrocortisone Versus Placebo in Dopamine-Treated Hypotensive Neonates Undergoing Hypothermia Treatment for Hypoxic–Ischemic Encephalopathy

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Objective To investigate whether hydrocortisone supplementation increases blood pressure and decreases inotrope requirements compared with placebo in cooled, asphyxiated neonates with volume-resistant hypotension.

Study design A double-blind, randomized, placebo-controlled clinical trial was conducted in a Level III neonatal intensive care unit in 2016-2017. Thirty-five asphyxiated neonates with volume-resistant hypotension (defined as a mean arterial pressure [MAP] < gestational age in weeks) were randomly assigned to receive 0.5 mg/kg/6 hours of hydrocortisone or placebo in addition to standard dopamine treatment during hypothermia.

Results More patients reached the target of at least 5-mm Hg increment of MAP in 2 hours after randomization in the hydrocortisone group, compared with the placebo group (94% vs 58%, $P = .02$, intention-to-treat analysis). The duration of cardiovascular support ($P = .001$) as well as cumulative ($P < .001$) and peak inotrope dosage ($P < .001$) were lower in the hydrocortisone group. In a per-protocol analysis, regression modeling predicted that a 4-mm Hg increase in MAP in response to hydrocortisone treatment was comparable with the effect of 15 μg/kg/min of dopamine in this patient population. Serum cortisol concentrations were low before randomization in both the hydrocortisone and placebo groups (median 3.5 and 3.3 μg/dL, $P = .87$; respectively), suggesting inappropriate adrenal function. Short-term clinical outcomes were similar in the 2 groups.

Conclusions Hydrocortisone administration was effective in raising the blood pressure and decreasing inotrope requirement in asphyxiated neonates with volume-resistant hypotension during hypothermia treatment. *(J Pediatr 2019; ■:1-7)*.

Trial registration ClinicalTrials.gov: NCT02700828.

Therapeutic hypothermia has become the standard of care treatment to improve morbidity and mortality in infants with hypoxic–ischemic encephalopathy (HIE).[1,2] Maintenance of normal heart function and systemic blood flow is important to restore adequate cerebral blood flow.[1] Asphyxiated neonates often present with multiorgan failure and systemic hypotension,[3] and treatment of cardiovascular impairment is a challenge in this clinical setting.

The pathophysiology of hemodynamic instability in patients with HIE is complex: asphyxia-associated myocardial ischemia, vasoregulatory impairment, and the direct effects of therapeutic hypothermia (sinus bradycardia, increased vascular resistance) all may play a role.[4] As a result, infants undergoing therapeutic hypothermia frequently present with decreased cardiac output[5] and hypotension, in addition to hypovolemia[6]; all of these may lead to systemic and brain hypoperfusion. Although the cardiovascular response to catecholamine therapy is blunted during therapeutic hypothermia,[7] infants often receive vasopressor or inotropic support.

Relative adrenal insufficiency, a condition characterized by inadequately low (<15 μg/dL) cortisol concentration in an acute illness setting, is a biologically plausible underlying etiology in patients with refractory hypotension.[8,9] We previously described the association of hypotension with low serum cortisol values[10] in asphyxiated neonates. Although hydrocortisone treatment improves blood pressure in other critically ill populations (infants born preterm and at term,[11-13] pediatric patients,[14] and adults[15,16]), the effects on hemodynamic stability in asphyxiated infants have not been studied systematically.

HIE	Hypoxic–ischemic encephalopathy
ITT	Intention-to-treat
MAP	Mean arterial pressure
PP	Per protocol

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In the present study, we hypothesized that asphyxiated neonates undergoing therapeutic hypothermia who develop volume-resistant hypotension have a degree of adrenal insufficiency that might contribute to their circulatory compromise. Therefore, we performed a randomized clinical trial to compare the effects of low-dose hydrocortisone supplementation vs placebo with standard dopamine therapy in both arms.

Methods

Study Design and Patient Population

This was a prospective, double-blind, randomized, placebo-controlled study that was conducted in a single center. Thirty-five asphyxiated infants with hypotension during therapeutic hypothermia were recruited prospectively between February 2016 and November 2017. Ethical permission for the study was obtained from the Scientific and Medical Research Council Ethics Committee of Hungary (5705-1/2016/EKU). The study was registered with ClinicalTrials.gov (NCT02700828). An external Data and Safety Monitoring Board, consisting of independent neonatologists, reviewed the clinical data after the first one-half of patient enrollment was accomplished and permitted the continuation of the study.

All patients were outborn and admitted to the neonatal intensive care unit at the 1st Department of Pediatrics, Semmelweis University. Inclusion criteria were (1) gestational age of ≥36 weeks, (2) provision of whole-body hypothermia treatment (as described by Azzopardi et al[17]), (3) presence of systemic hypotension (defined as a mean arterial pressure [MAP] less than the gestational age in weeks) despite administration of volume expanders, and (4) written informed parental consent. Infants were excluded if they had received (1) single or combined vasopressor−inotrope therapy before randomization, (2) presented with congenital abnormalities, and (3) had a hematocrit level ≤35%.

Eligible patients randomly were assigned to receive 0.5 mg/kg hydrocortisone or placebo intravenously every 6 hours during therapeutic hypothermia, based on recent recommendations.[18] Simultaneously, intravenous dopamine treatment was initiated in all patients to ensure timely management of hypotension. The last dose of the study drug was given during the 7-hour period of rewarming phase after the 72-hour therapeutic hypothermia. The primary outcome of the present study was defined as the proportion of patients who reached at least 5-mm Hg increase of MAP in 2 hours after randomization. Sample size calculation demonstrated that a total of 32 patients, 16 in each treatment arm, was needed to show the difference in MAP with hydrocortisone administration vs placebo, with a power of 80%, using a 2-sided $P = .05$. Sample size calculation was based on our previous observational data showing a 5-mm Hg increase in MAP in the presence of dopamine, 2-6 hours after hydrocortisone administration. Secondary outcomes included initial serum cortisol levels; duration, cumulative, and maximum dose of inotrope therapy; and diuresis.

Management of Low Systemic Blood Pressure

In asphyxiated neonates with hypotension, an indwelling umbilical or peripheral radial arterial line was placed and blood pressures were recorded every 30 minutes. The diagnosis of systemic hypotension was established using the definition by Baker et al.[19] One or two doses of fluid boluses (10 mL/kg per dose over 15 minutes) were given initially to correct presumed hypovolemia. If volume expansion was deemed unsuccessful in maintaining blood pressure, the infant randomly was assigned to receive hydrocortisone or placebo. Simultaneously, dopamine infusion was started at a rate of 6 μg/kg/min, and, if necessary, the dose was increased in 2 μg/kg/min increments up to 20 μg/kg/min. The use of dobutamine was reserved for patients with poor cardiac contractility on echocardiography, which was performed by a pediatric cardiologist. Weaning of inotropes was initiated based on the attending neonatologists' decision, who were blinded to the study.

Serum cortisol levels were measured at randomization, and every 24 hours thereafter, using electrochemiluminescent immunoassays (Elecsys, Cobas E411; Roche, Basel, Switzerland). The clinical management was not influenced by the cortisol levels, as the clinicians did not see the results until the end of the study.

All infants received a morphine infusion (10 μg/kg/h, Morfina Cloridrato Monico; Monico SPA, Venezia/Mestre, Italy) during therapeutic hypothermia. Phenobarbital (Gardenal; Sanofi Winthrop Industrie, Maisons-Alfort, France) was administrated as a first-line anticonvulsive drug in cases of clinical or electrophysiological seizures. Other details of drug preparation, clinical management, and data collection are described in the Online Supplementary Material.

Statistical Analyses

A computer randomization procedure (computer-generated random numbers with block randomization technique) guaranteed the equal number of patients in both treatment arms. New patients were computer-randomized for enrollment after the exclusion of 3 cases from the placebo group to ensure the target patient number on each arm.

Descriptive statistics were expressed as median and IQRs or number and percentage. The Barnard exact test, χ^2 test, Mann−Whitney U test, and Wilcoxon signed rank test were used to compare clinical characteristics and outcomes between treatment groups as appropriate. Both an intention-to treat (ITT) and a per-protocol (PP) analysis were performed. Regression modeling was performed only on the PP dataset to predict MAP, heart rate, and pulse pressure (systolic − diastolic blood pressure difference) using a repeated-measures linear mixed-effect model with first-order autoregressive within-group correlation structure fitted by maximizing the restricted log-likelihood. The following variables were considered to have fixed effects: hydrocortisone treatment, dosage of dopamine and dobutamine (μg/kg/min as a continuous variable), Thompson encephalopathy score predicting adverse neurologic outcome[20] (categorized as low, medium, or high), time, baseline heart

Table I. Clinical characteristics of the study population based on the ITT and PP analysis

Variables	ITT analysis			PP analysis	
	Hydrocortisone group (n = 16)	Placebo group (n = 19)	*P* value	Placebo group (n = 16)	*P* value
Gestational age, wk	39 [38; 40]	39 [38; 40]	.68	40 [38; 40]	.41
Birth weight, g	3625 [3390; 3663]	3500 [3250; 3850]	.76	3440 [3200; 3725]	.83
Sex (female/male), n (%)	2 (12.5)/14 (87.5)	10 (53)/9 (47)	**.01**	9 (56)/7 (44)	**.009**
Mode of delivery (vaginal/cesarean), n (%)	9 (56)/7 (44)	8 (42)/11 (58)	.40	6 (37.5)/10 (62.5)	.29
Apgar scores					
1 min	3 [1; 5]	3 [2; 5]	.80	4 [2; 5]	.63
5 min	5 [4; 6]	5 [4; 7]	.76	5.5 [4; 7]	.60
10 min	7 [6; 7]	7 [6; 7]	.88	7 [7; 7]	.39
First blood gas analysis					
pH	7.0 [6.9; 7.1]	7.0 [6.9; 7.1]	.61	7.0 [6.9; 7.1]	.93
pCO_2, mm Hg	69 [51; 75]	61 [45; 74]	.37	57 [40; 65]	.09
Base deficit, mmol/L	−16.0 [−13.0; −16.8]	−15.0 [−12.5; −20.8]	1.00	−14.6 [−11.0; −19.6]	.82
HCO_3^-, mmol/L	15.3 [13.6; 16.7]	11.2 [10.0; 17.7]	.26	11.2 [10.2; 17.5]	.23
Serum lactate, mmol/L	13.9 [11.0; 15.8]	12.6 [11.3; 17.0]	.96	12.6 [11.4; 18.0]	.88
Glucose, mmol/L	4.4 [3.1; 5.7]	5.7 [2.9; 7.8]	.16	5.9 [4.9; 7.9]	.07
Age at the onset of hypothermia treatment, h	2.8 [2.2; 3.3]	2.4 [1.7; 2.9]	.39	2.3 [1.7; 3.1]	.55
Lowest systolic BP, mm Hg	47 [45; 48]	44 [41; 48]	.12	44 [41; 48]	.21
Lowest mean BP, mm Hg	34 [31; 37]	34 [30; 36]	.62	34 [31; 36]	.92
Lowest diastolic BP, mm Hg	26 [22; 29]	27 [23; 30]	.48	27 [25; 29]	.29
Lowest serum sodium level, mmol/L	134 [133; 135]	136 [134; 138]	**.03**	136 [134; 137]	.11
Age at randomization, h	10.8 [8.1; 18.0]	14.3 [9.0; 20.2]	.55	14.8 [9.7; 21.8]	.26
Serum cortisol concentration at randomization, μg/dL	3.5 [2.2; 14.5]	3.8 [2.5; 15.0]	.68	3.3 [2.4; 11.3]	.87
Unilateral adrenal bleeding, n (%)	1 (6)	2 (11)*	.62	1 (7)†	.96
Clinical severity according to the SNAP-II score before randomization, n (%)					
Mild	7 (43.75)	6 (31.5)	.26	6 (37.5)	.66
Moderate	7 (43.75)	6 (31.5)		6 (37.5)	
Severe	2 (12.5)	7 (37)		4 (25)	
Thompson risk score for adverse neurodevelopmental outcome, n (%)					
Low/0-10 points	10 (62.5)	10 (53)	.84	10 (62.5)	1.00
Medium/11-14 points	4 (25)	6 (31)		4 (25)	
High/≥15 points	2 (12.5)	3 (16)		2 (12.5)	

BP, blood pressure; HCO_3^-, bicarbonate; pCO_2, partial pressure of carbon dioxide; *SNAP-II*, Score for Neonatal Acute Physiology, second edit.
Data shown as median and IQR. See text for details.
Statistically significant *P* values are set in bold.
*n = 18.
†n = 15.

rate, and baseline systolic−diastolic blood pressure difference (measured at zero time point). Statistical tests were performed using IBM SPSS Statistics 22.0 (IBM Corp, Armonk, New York) or R Statistical Software (R Foundation for Statistical Computing, Vienna, Austria). Graphs were plotted with GraphPad Prism, Version 6.01 (GraphPad Software, San Diego, California). The level of significance was set at .05.

Results

During the 22-month study period, of the 67 asphyxiated infants eligible for initial assessment, 35 infants with HIE met the inclusion criteria and were enrolled (**Figure 1**; available at www.jpeds.com). Three infants from the placebo group subsequently were excluded due to critical deterioration (severe complications included pulmonary hypertension, acute kidney failure treated with continuous venovenous hemofiltration, and hypertrophic cardiomyopathy) and received hydrocortisone, thus breaking the study protocol. Accordingly, we performed both an ITT and a PP analysis on the dataset.

The clinical characteristics of the study population are summarized in **Table I**. Baseline characteristics of the hydrocortisone and placebo groups were comparable, although there was a difference in sex distribution.

The results of the study were similar for the ITT and the PP analyses (**Table II**). For the primary outcome, more patients reached at least a 5-mm Hg increase in MAP in 2 hours after randomization in the treatment group than in the control group in both the ITT analysis ($P = .02$) and the PP analysis ($P = .04$). We analyzed the changes of blood pressure and inotrope dosage throughout the study period and plotted the averaged values in 6-hour epochs starting at the administration of the first dose of hydrocortisone or placebo (time point 0, **Figure 2**; excluded patients are shown in **Figure 3** [available at www.jpeds.com]). MAP increased between 0-1 hour after randomization in both groups (from a median of 36.5 to 55.5 mm Hg in the

Table II. Clinical outcomes based on the ITT and PP analysis

Variables	Hydrocortisone group (n = 16)	ITT analysis: Placebo group (n = 19)	ITT analysis: *P* value	PP analysis: Placebo group (n = 16)	PP analysis: *P* value
Cardiovascular					
Primary outcome: 5-mm Hg increase at 120 min, n (%)	15 (94)	11 (58)	**.02**	10 (63)	**.04**
Duration of inotrope therapy, h*	47 [18; 78]	96 [73; 107]	**.001**	92 [70; 102]	**.004**
Cumulative dose of inotrope therapy, mg/kg*	10 [3; 27]	51 [30; 57]	**<.001**	51 [27; 57]	**.001**
Maximum dose of inotrope therapy, μg/kg/min*	6 [6; 9]	16 [10; 20]	**<.001**	12 [9; 17]	**.002**
Neurologic					
aEEG background activity normalization within 48 h, n (%)	10 (63)	14 (78)†	.33	13 (81)	.24
Convulsion on aEEG, n (%)	9 (56)	4 (21)	**.03**	4 (25)	.07
Anticonvulsant therapy, n (%)	8 (50)	5 (26)	.15	4 (25)	.14
Brain MRI abnormality					
HIE, n (%)	9 (56)	8 (47)‡	.60	6 (40)§	.37
Intraparenchymal cerebral hemorrhage, n (%)	3 (19)	3 (18)‡	.94	2 (13)§	.68
Time of MRI scan, day of life	6 [5; 7]	5 [5; 6]‡	.79	5 [5; 7]§	.78
Respiratory					
Duration of mechanical ventilation, d	4 [4; 5]	4 [4; 5]	.71	4 [4; 5]	.91
Renal					
Oliguria, anuria, n (%)	3 (19)	5 (26)	.60	3 (19)	1.00
Infection					
Culture-proven sepsis, n (%)	1 (6)	1 (5)	.90	0 (0)	.31
Antibiotic treatment, d	2 [1; 4]	3 [2; 7]	.22	3 [2; 6]	.30
Hypoglycemic episodes, n (%)	9 (56)	12 (63)	.68	10 (63)	.72
Hyperglycemic episodes, n (%)	0 (0)	0 (0)	1.00	0 (0)	1.00
Gastrointestinal					
GI bleeding, perforation, n (%)	0 (0)	0 (0)	1.00	0 (0)	1.00
Time until exclusive enteral nutrition, day of life	7 [7; 9]	8 [7; 9]	.71	7 [6; 9]	.93
Others					
Discharge to home/other hospital, n (%)	12 (75)/4 (25)	8 (44)/10 (56)	.07	7 (44)/9 (56)	.07
Length of hospitalization, d	14 [11; 21]	16 [10; 20]	.94	17 [10; 19]	.90
In-hospital mortality, n (%)	0 (0)	1 (5)	.35	0 (0)	1.00

aEEG, amplitude-integrated electroencephalography; *GI*, gastrointestinal; *MRI*, magnetic resonance imaging.
Data shown as median and IQR. See text for details.
Statistically significant *P* values are set in bold.
*Inotrope therapy: dopamine plus dobutamine therapy. Oliguria, anuria: urine output <1 mL/kg/h during the study period. Hypoglycemia: blood glucose <2.6 mmol/L at any time during the study period. Hyperglycemia: need for insulin treatment during the study period.
†n = 18.
‡n = 17.
§n = 15.

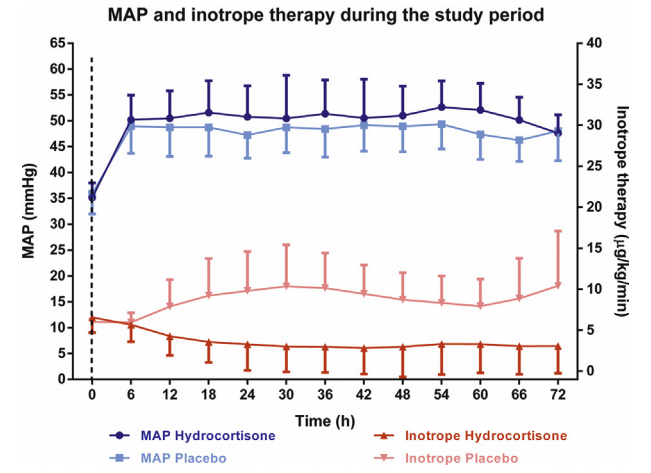

Figure 2. The trends of the average mean arterial pressure (left y axis, in *blue*, mm Hg, mean ± SD) and inotrope therapy (right y axis, in *red*, μg/kg/min, mean ± SD) are shown in 6-hour epochs. Time "0" is the start of hydrocortisone or placebo treatment.

hydrocortisone group and to 51.5 mm Hg in the placebo group) and remained relatively constant thereafter. Statistical modeling for blood pressure trends revealed that between 1 and 72 hours, the hydrocortisone group had greater MAP, by an average of 4 mm Hg (β = 4.06, P = .045, repeated-measures linear mixed-effect model). Because both groups received dopamine for cardiovascular support, and it was escalated and weaned during the study period as needed, we included it in our model as a continuous variable. Dopamine, as expected, had a significant effect on MAP (P < .001). The regression equation predicted that an increase of 4 mm Hg in MAP, corresponding to the effect of hydrocortisone administration as per the study protocol, was comparable with 15 μg/kg/min dopamine treatment (**Table III**).

Heart rate trended greater over time in the placebo group compared with the hydrocortisone group (**Figure 4** and **Table IV**; available at www.jpeds.com). Based on the regression modeling, the use of hydrocortisone was associated with a 13 beats/minute decrease in heart rate compared with the placebo group (P < .001), likely related

Table III. Summary of the trend analysis of blood pressure changes in the hydrocortisone and placebo groups

Variables	β	95% CI	P value
Intercept	46.92	43.80-50.04	<.001
Hydrocortisone treatment	4.06	1.48-6.64	.045
Inotrope therapy	0.28	0.12-0.43	<.001
Thompson encephalopathy score	−0.61	−2.31 to 1.09	.47

β, regression coefficient.
A repeated-measures linear mixed-effect model was run for trend analysis of mean arterial pressure values between 1 and 72 hours after randomization. Hydrocortisone treatment (as 1 vs placebo as 0), dosage of inotropes (in μg/kg/min as a continuous variable), and Thompson encephalopathy score predicting adverse neurologic outcome (low [0-10 points] as 1, medium [11-14 points] as 2, high [≥15 points] as 3) were included as variables with fixed effects. The regression modeling predicted that the use of hydrocortisone was associated with a 4-mm Hg ($\beta = 4.06$) increase in MAP compared with the placebo group ($P = .045$) and 10 μg/kg/min inotrope treatment increased the MAP by 2.8 mm Hg ($\beta = 0.28/1$ μg/kg/min inotrope support) ($P < .001$).

to the lower dosage of dopamine used. The regression model predicted that 10 μg/kg/min inotrope treatment increased the heart rate by 5.4 beats/min ($P = .001$).

We also analyzed the systolic−diastolic blood pressure difference in the 2 treatment groups and found that time elapsed during the study period or the dosage of inotrope therapy had no effect ($P = .09$ and .64, respectively; **Figure 5** and **Table V**; available at www.jpeds.com). The pressure gradient, however, was greater, by 2.2 mm Hg in the hydrocortisone treatment group ($P = .02$), a finding that was already present at baseline.

The duration of cardiovascular support, cumulative, and peak inotrope dosage were all lower in the hydrocortisone group (**Table II**). Besides the 3 excluded patients, only 2 infants from the placebo group received dobutamine therapy in addition to dopamine based on echocardiography findings. Other clinical outcomes were similar in the hydrocortisone and placebo groups (**Table II**).

Cortisol levels were evaluated in the PP analysis, excluding patients who received hydrocortisone outside of study protocol. Baseline median serum cortisol values at enrollment were low in both groups (Time 0) and 12 of 16 patients in both treatment arms had serum cortisol levels <15 μg/dL ($P = 1.00$; **Table VI** [available at www.jpeds.com]). The cortisol levels in the placebo group decreased during the study period (**Table VI**, $P = .02$; Wilcoxon signed rank test).

Discussion

The results of our randomized controlled trial showed that hydrocortisone administration was effective in raising the blood pressure of patients with HIE with volume-resistant hypotension during therapeutic hypothermia. A greater proportion of patients reached at least 5-mm Hg increase of MAP within 2 hours of drug administration. In addition, adjunctive dopamine therapy was reduced and inotropes were weaned off sooner in the hydrocortisone treatment group, compared with the placebo group. On the basis of our findings, a larger multicenter trial may be warranted to confirm or disprove the beneficial effects of hydrocortisone therapy in patients with HIE with volume-resistant hypotension.

Perinatal hypoxic−ischemic injury results in transient myocardial ischemia, cardiovascular instability, and systemic hypotension in 42%-81% of asphyxiated neonates.[17,21-23] Both the primary hypoxic insult and redistribution of blood flow may lead to reduced myocardial perfusion and decreased myocardial performance resulting in systemic hypotension despite the vasoconstrictor effects of therapeutic hypothermia.[4] Furthermore, the hypoxic insult may affect the adrenal gland itself[24] or adrenal hemorrhage could worsen the impaired adrenal performance, leading to low serum cortisol levels and increased risk of heart dysfunction.[25]

Vasopressor−inotropes, when given at inappropriately high doses, may be counterproductive in asphyxiated infants with compromised myocardial function, especially because therapeutic hypothermia itself raises systemic vascular resistance with consequential exposure to increased afterload.[6] For example, although the MAP increases, cardiac output may remain low, leading to sustained hypoperfusion of vital organs, which might not be recognized clinically. By avoiding high doses of dopamine, cardiovascular physiology may be optimized, and symptoms of low cardiac output may be prevented. Finally, it is plausible that a 5-mm Hg mean blood pressure increase in hypotensive asphyxiated neonates may contribute to more appropriate cerebral and other organ blood flow. Physiological sinus bradycardia has been observed during therapeutic hypothermia,[26] which is considered acceptable for the reduced metabolic rate due to both the injury and therapeutic hypothermia. We found elevated heart rate in our placebo group, which could be the consequence of greater doses of dopamine treatment or a compensatory response to lower cardiac output. We speculate that this relative tachycardia may negatively impact heart function and coronary perfusion and that avoiding dopamine therapy may be beneficial. In addition, the duration and the dose of inotrope administration may negatively affect the introduction of enteral feeding and the length of hospitalization among other short-term outcomes. Therefore, we consider our finding of decreased inotrope demand in the hydrocortisone treatment group highly relevant in this clinical setting.

Critically ill newborns who are born at term, frequently present with relative adrenal insufficiency during the first week after delivery.[27] In asphyxiated infants, in addition to the suspected hypoxic adrenal injury, the hypothalamic–pituitary–adrenal axis also may be in a transient refractory state during and after the transitional period.[8] Admittedly, the normal range of serum cortisol levels is currently unknown in this patient population, and the definition of relative adrenal insufficiency is also controversial. Median cortisol levels were low (~3.5 μg/dL) in our patient population before randomization, suggesting that the studied infants might have had some degree of adrenal insufficiency.[8,9,28] Of note is that serum cortisol levels decreased even further in the placebo group during the study period with a nadir on day 3.

Hydrocortisone administration resulted in high serum cortisol levels, and this might have been due, at least in part, to decreased drug metabolism in patients with HIE.[29] Clearly, further studies are needed to describe the hydrocortisone pharmacokinetics in this patient population to determine the optimal dosing of the drug. Nevertheless, the rationale behind hydrocortisone therapy in cases of volume-resistant hypotension is that it may directly address the underlying etiology, contrary to inotropes, which only provide symptomatic treatment.

Previous studies of hydrocortisone administration have shown effectiveness in raising systemic blood pressure and enhancing hemodynamic stability in other populations, including infants born preterm and at term,[13] infants with heart surgery,[30] pediatric and adult patients with septic shock.[14,31] Hydrocortisone treatment has not been studied systematically in asphyxiated newborns, although it is used frequently as a rescue therapy in vasopressor-resistant hypotension, and it appears as a treatment option in clinical review articles.[24] In general, corticosteroid therapy stabilizes the cardiovascular status through genomic and non-genomic receptor signaling pathways,[32] leading to improved adrenergic receptor function, increased plasma concentration of catecholamines, and improved endothelial integrity.[33] The non-genomic actions take effect within 2-6 hours and may increase blood pressure independently from the actual serum cortisol level.[33] Thus, an increase of blood pressure can be expected soon after the start of hydrocortisone supplementation.[13,19]

Steroid supplementation should be considered carefully in neonates due to its potential effects on neurodevelopment.[34] Adverse outcomes have been reported in connection with glucocorticoids. The use of early dexamethasone to prevent bronchopulmonary dysplasia in neonates born preterm has been associated with abnormal brain development and an increased risk of cerebral palsy.[35] Although limited, current data have not found evidence for adverse neurodevelopmental effects of hydrocortisone,[36,37] and a potential benefit after hydrocortisone treatment has been suggested.[38] Still, to ensure the safety of hydrocortisone treatment in our patient population of neonates born at term with HIE, we are conducting a follow-up substudy focused on neurodevelopmental outcomes at 2 years of age.

There are limitations to this study that should be noted. First, this was a clinical trial with a relatively small sample size, and patients receiving catecholamine therapy on admission were excluded. Both the treatment and placebo groups received 6 μg/kg/min dopamine therapy to ensure the timely management of hypotension in all neonates with HIE. Thus, hydrocortisone effects alone could not be directly discerned in our study; however, regression modeling confirmed that hydrocortisone treatment was comparable with greater dosage dopamine (15 μg/kg/min) treatment in terms of the magnitude of blood pressure changes. The lack of consistent echocardiography data to interrogate the impact on heart function and cardiac loading conditions limits thoughtful mechanistic interrogation. It is plausible that there may be unique subgroups of patients who may benefit from myocardial support, adrenal support, as well as vascular tone modification. Furthermore, due to cross-reaction in the assay used, the measured cortisol levels include endogenous cortisol plus hydrocortisone in the treatment group and only endogenous cortisol in the placebo group. Of note, cortisol levels in the placebo group were very low, suggesting that the greater values in the treatment group reflect the presence of exogenous hydrocortisone. Finally, the long-term neurodevelopmental follow-up findings are still awaited in our patient population. Short-term outcomes, however, including hospitalization length and discharge data, were reassuring. If our results are confirmed by a larger, multicenter trial that includes neurodevelopmental follow-up as one of the primary outcome measures, our data support earlier use of hydrocortisone in patients with HIE with hemodynamic instability. ■

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Data Statement

Data sharing statement available at www.jpeds.com

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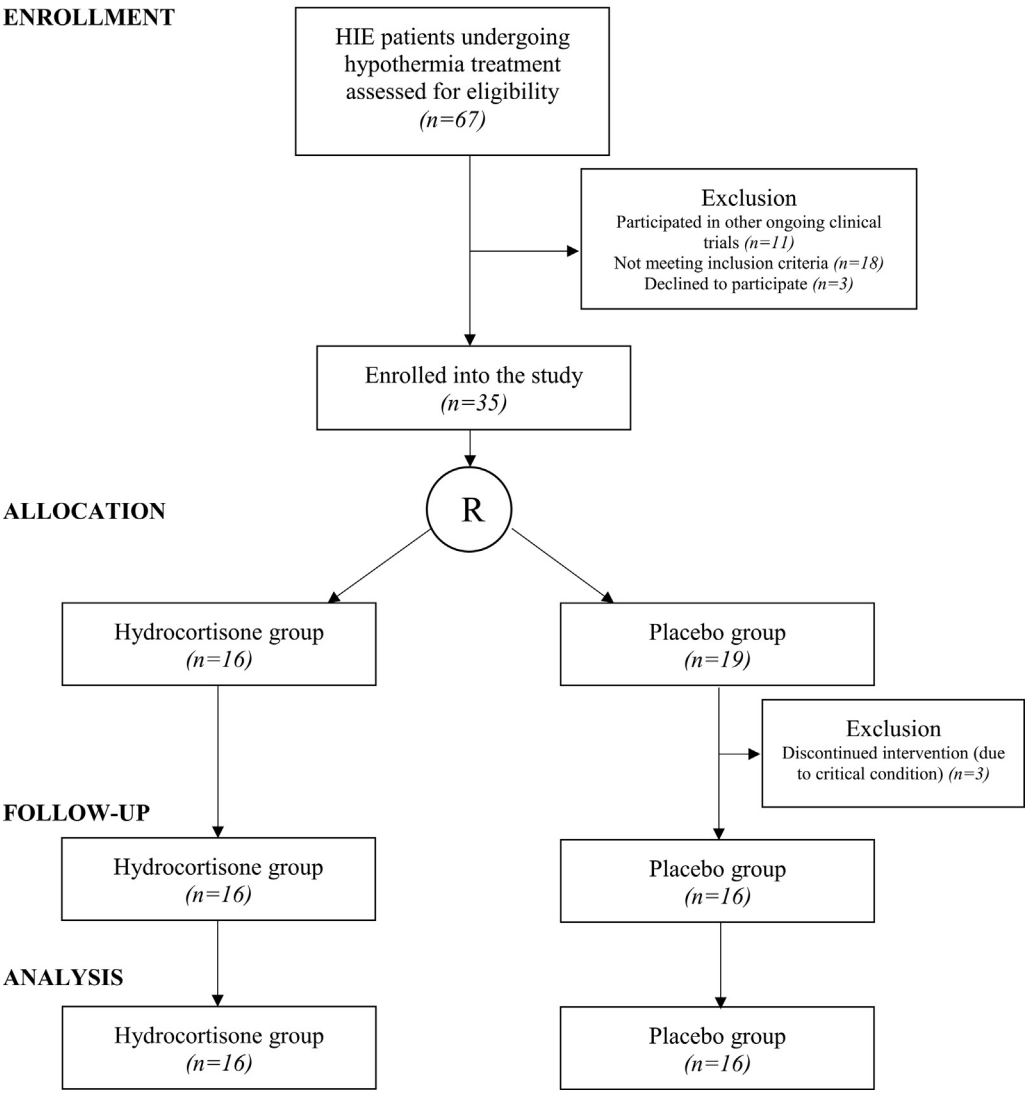

Figure 1. Patients with hypoxic-ischemic encephalopathy. *R*, randomization.

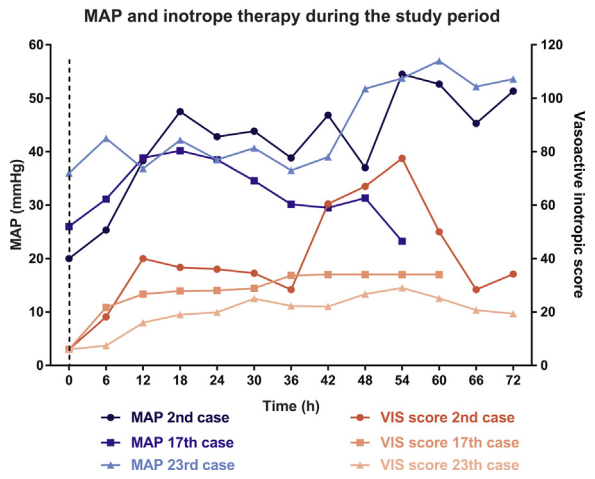

Figure 3. The average mean arterial pressure of the 3 excluded cases (left y axis, in *blue*, mm Hg) and VIS (right y axis, in *red*) are shown in 6-hour epochs. Time "0" is the start of placebo treatment. VIS score = dopamine (μg/kg/min) + dobutamine (μg/kg/min) + 100 × epinephrine (μg/kg/min) + 100 × norepinephrine (μg/kg/min) + 10 × milrinone (μg/kg/min) + 10 000 × vasopressin (U/kg/min). *VIS*, vasoactive inotropic score.

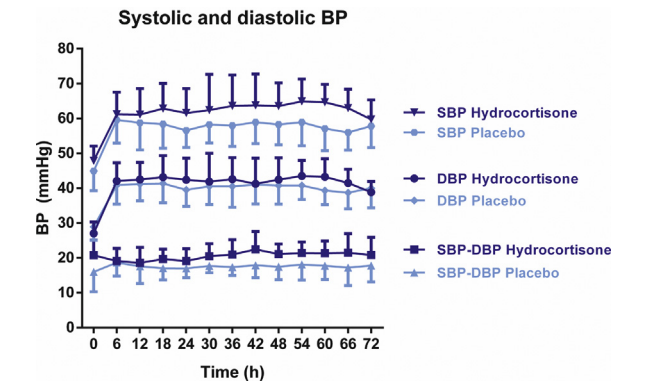

Figure 5. Trends of SBP, DBP, and SBP-DBP difference (mm Hg, mean ± SD) are shown in 6-hour epochs. Time "0" is the time of randomization, coinciding with the start of hydrocortisone or placebo treatment. *BP*, blood pressure; *DBP*, diastolic blood pressure; *SBP*, systolic blood pressure.

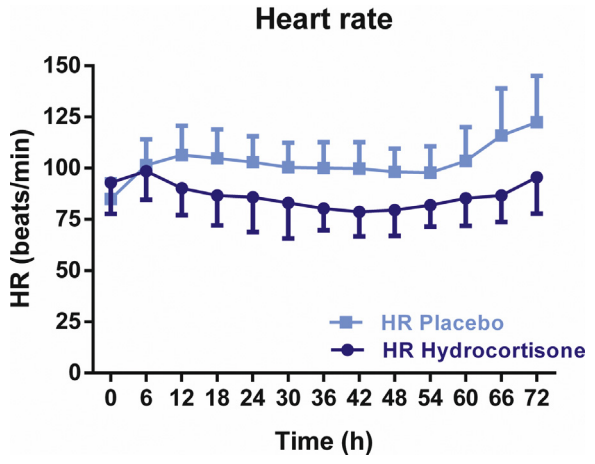

Figure 4. Trends of the HR (beats/min, mean ± SD) are shown in 6-hour epochs. Time "0" is the time of randomization, coinciding with the start of hydrocortisone or placebo treatment. *HR*, heart rate.

Table IV. Summary of the trend analysis of heart rate in the hydrocortisone and placebo groups

Variables	β	95% CI	*P* value
Intercept	55.53	36.06-75.00	<.001
Hydrocortisone treatment	−13.16	−19.48 to −6.83	<.001
Heart rate at 1 h after randomization	0.43	0.22-0.64	.001
Time	0.06	−0.06 to 0.17	.35
Inotrope therapy	0.54	0.23-0.85	.001

A repeated-measures linear mixed-effect model was run for trend analysis of heart rate between 1 and 72 hours after randomization. Hydrocortisone treatment (as 1 vs placebo as 0), baseline heart rate at 1 hour after randomization (in beats/min), time (in hours), and dosage of inotropes (in μg/kg/min as a continuous variable) were included as variables with fixed effects.

The regression modeling predicted that the use of hydrocortisone was associated with a 13 beats/min ($\beta = -13.16$) decrease in heart rate compared with the placebo group ($P < .001$) and 10 μg/kg/min inotrope treatment increased the heart rate by 5.4 beats/min ($\beta = 0.54$/1 μg/kg/min inotrope support) ($P = .001$).

Table V. Summary of the trend analysis of SBP-DBP difference, or pulse pressure, in the hydrocortisone and placebo groups

Variables	β	95% CI	*P* value
Intercept	12.52	9.27-15.76	<.001
Hydrocortisone treatment	2.16	0.37-3.95	.02
SBP-DBP difference at 1 h after randomization	0.20	0.07-0.34	.003
Time	0.03	−0.01 to 0.06	.09
Inotrope therapy	0.02	−0.07 to 0.11	.65

DBP, diastolic blood pressure; *SBP*, systolic blood pressure.
A repeated-measures linear mixed-effect model was run for trend analysis of SBP-DBP difference, or pulse pressure, between 1 and 72 hours after randomization. Hydrocortisone treatment (as 1 vs placebo as 0), baseline SBP-DBP difference at 1 hour after randomization (in mm Hg), time (in hours), and dosage of inotropes (in μg/kg/min as a continuous variable) were included as variables with fixed effects.
The regression modeling predicted that he use of hydrocortisone was associated with a 2.2-mm Hg (β = 2.16) increase in pulse pressure compared with the placebo group (P = .02).

Table VI. Serum cortisol measurements

Timepoints	Time of measurements (hours of life)	Cortisol levels in the hydrocortisone group (μg/dL, n = 16)	Cortisol range	Cortisol levels in the placebo group (μg/dL, n = 16)	Cortisol range
Time 0 (randomization)	13.9 [6; 21]	3.5 [2.2; 14.5]	0.5-41.6	3.3 [2.4; 11.3]	0.9-54.7
Time 1	24 [24; 36]	62.4 [30.7; 74.6]	15.7-382.8	2.0 [1.5; 4.6]	0.7-27.2
Time 2	48 [48; 72]	120.1 [85.6; 254.9]	22.6-598.7	1.0 [0.7; 1.3]	0.3-28.1
Time 3	72 [72; 72]	80.9 [49.8; 137.6]	16.0-417.7	0.8 [0.6; 2.5]	0.5-15.0

Data are shown based on the PP analysis.
The excluded 3 infants had a median cortisol level of 13.2 [8.6; 15.0] μg/dL at Time 0.