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A Double-Blind, Randomized, Controlled Study of a “Stress Dose” of Hydrocortisone for Rescue Treatment of Refractory Hypotension in Preterm Infants

Pak C. Ng, FRCPCH, MD^a, Cheuk H. Lee, FRCP (Edin)^a, Flora Liu Bnur^a, Iris H.S. Chan, PhD^b, Anthony W.Y. Lee, MSc^c, Eric Wong, MSc^d, Hin B. Chan, MRCP (UK)^e, Christopher W.K. Lam, PhD^b, Benjamin S.C. Lee, PhD^c, Tai F. Fok, FRCPCH, MD^a

^aDepartment of Pediatrics, Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong; ^bDepartment of Chemical Pathology, Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong; ^cPharmacy, Prince of Wales Hospital, Hong Kong; ^dCenter of Epidemiology and Biostatistics, The Chinese University of Hong Kong, Hong Kong; ^eDepartment of Pediatrics and Adolescent Medicine, United Christian Hospital, Hong Kong

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ABSTRACT

OBJECTIVE. To assess the effectiveness of a “stress dose” of hydrocortisone for rescue treatment of refractory hypotension and adrenocortical insufficiency of prematurity in very low birth weight (VLBW) infants. We hypothesized that significantly more VLBW infants who were receiving dopamine $\geq 10 \mu\text{g}/\text{kg}$ per min could wean off vasopressor support 72 hours after treatment with hydrocortisone.

METHODS. A double-blind, randomized, controlled study was conducted in a university neonatal center. Forty-eight VLBW infants who had refractory hypotension and required dopamine $\geq 10 \mu\text{g}/\text{kg}$ per min were randomly assigned to receive a stress dose of hydrocortisone (1 mg/kg every 8 hours for 5 days; $n = 24$) or an equivalent volume of the placebo solution (isotonic saline; $n = 24$).

RESULTS. The baseline clinical characteristics were similar between the groups. Serum cortisol concentrations were very low immediately before randomization in both groups of infants. Significantly more VLBW infants who were treated with hydrocortisone weaned off vasopressor support 72 hours after starting treatment. The use of volume expander, cumulative dose of dopamine, and dobutamine were significantly less in hydrocortisone-treated infants compared with control infants. In addition, the median duration of vasopressor treatment was halved in hydrocortisone-treated patients. Two versus 11 infants in the hydrocortisone and control groups required a second vasopressor for treatment of refractory hypotension. The trend (linear and quadratic) of the mean arterial blood pressure was also significantly and consistently higher in hydrocortisone-treated infants.

CONCLUSIONS. A stress dose of hydrocortisone was effective in treating refractory hypotension in VLBW infants. Although routine and prophylactic use of systemic corticosteroids could not be recommended because of their potential adverse effects, this relatively low dose of hydrocortisone would probably be preferable to high-dose dexamethasone for treatment of refractory hypotension in emergency and life-threatening situations.

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Key Words

adrenocortical insufficiency, hydrocortisone, hypotension, preterm infants

Abbreviations

VLBW—very low birth weight
HPA—hypothalamic-pituitary-adrenal
BP—blood pressure

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Address correspondence to Prof Pak C. Ng, Department of Pediatrics, Level 6, Clinical Sciences Building, Prince of Wales Hospital, Shatin, New Territories, Hong Kong. E-mail: pakcheungng@cuhk.edu.hk

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SYSTEMIC HYPOTENSION IS a common complication of sick preterm infants and may be associated with major adverse outcomes, including intraventricular hemorrhage, neurodevelopmental morbidity, and mortality.¹⁻⁴ The cause of hypotension in preterm infants is diverse and multifactorial. In the past decade, it has been increasingly recognized from animal studies⁵ and clinical observations that a significant proportion of very low birth weight (VLBW) infants may experience severe hypotension that is refractory to both volume expanders and vasopressors but responds readily and effectively to corticosteroids, hydrocortisone, or dexamethasone, treatment.⁶⁻¹¹ Recent studies have demonstrated marked elevation of serum cortisol precursors' concentrations and low circulating level of cortisol in preterm infants under stress, suggesting that the underlying pathophysiology of systemic hypotension may be associated with an immature hypothalamic-pituitary-adrenal (HPA) axis secondary to intermediate enzyme deficiency and decreased capacity to synthesize cortisol.¹²⁻¹⁵ Functional assessment of the HPA axis with synthetic corticotropin¹⁶ and human corticotrophin releasing hormone^{10,17,18} further indicates that the pituitary gland is able to respond normally to human corticotrophin releasing hormone^{10,17,18} but there is inadequate cortisol release during the first 7 days of life.^{10,16-18} Adrenocortical insufficiency secondary to immature HPA axis, however, is transient. In majority of cases, both pituitary and adrenal glands are able to respond adequately to exogenous stimulation by day 14 of life,^{17,18} although in some extremely premature infants, the inadequate adrenocortical response may persist into the third week.¹⁵ The distinct pattern of cortisol response in sick newborn infants suggests that these infants may have suboptimal adrenocortical response to stress in early postnatal life, but it is likely that rapid adaptation of the HPA axis to extrauterine life results in sufficient cortisol secretion by the end of the second week in most patients. As the transient functional abnormality may contribute to the development of systemic hypotension in preterm newborns, the most logical approach for treating these infants is to replace the physiologic deficient hormone during the acute phase. Furthermore, extensive use of volume boluses may increase the likelihood of pulmonary edema and persistent ductal patency, and infusion of high-dose vasopressors may lead to decreases in organ perfusion as a result of the potential for causing severe peripheral vasoconstriction despite apparent improvements in the blood pressure (BP). The aim of this prospective, double-blind, randomized, controlled study was to assess the effectiveness of a "stress dose" of hydrocortisone (1 mg/kg per dose every 8 hours for 5 days) for rescue treatment of refractory hypotension in preterm, VLBW infants during the first week of life. We hypothesized that significantly more hypotensive infants who require dopamine ≥ 10 $\mu\text{g}/\text{kg}$ per minute could wean off vasopressor support 72

hours after treatment with hydrocortisone. The utilization of volume expanders and vasopressors after randomization in the first 14 days of life was determined and also used as indicators of treatment success. Serious short- and medium-term adverse effects of corticosteroids, including hyperglycemia/glycosuria, gastrointestinal complications, and systemic infection, were also monitored.

METHODS

Study Population

A total of 48 VLBW infants with refractory hypotension were recruited prospectively into the study within a 42-month period between June 2001 and November 2004. The inclusion criteria were (1) gestational age < 32 weeks, (2) birth weight < 1500 g, (3) systemic hypotension¹⁹ despite treatment with volume expanders (isotonic saline ≥ 30 mL/kg) and dopamine infusion ≥ 10 $\mu\text{g}/\text{kg}$ per minute within the first 7 days of life, (4) having an indwelling peripheral or umbilical arterial cannulae for continuous BP monitoring, and (5) written informed parental consent for carrying out the study. Infants were excluded when they had (1) major or lethal congenital or chromosomal abnormalities; (2) congenital heart defects (excluding patent ductus arteriosus); (3) postnatal systemic or inhaled corticosteroids for treatment of severe lung disease before receiving the trial drug; and (4) proven systemic infection or necrotizing enterocolitis or underwent major surgery before randomization. However, the use of antenatal corticosteroids did not preclude the infants from entering the study, as most of the mothers would have received such treatment to enhance fetal lung maturity. Each antenatal course consisted of 4 doses of 6 mg of dexamethasone (dexamethasone sodium phosphate; Weiner Pharma, GmbH, Rastatt, Germany) administered intravenously, 12 hours apart. Infants who required intubation and positive pressure ventilation received a standard course of surfactant (Surventa; Abbott Laboratories, North Chicago, IL; 2 doses of 4 mL/kg, given 12 hours apart) as rescue treatment for respiratory distress syndrome. VLBW infants who weighed ≤ 1250 g were given prophylactic indomethacin (Indocin; Merck & Co, West Point, Philadelphia, PA; 0.1 mg/kg intravenously within 6 hours of birth and then every 24 hours for 2 additional doses) for prevention of intraventricular hemorrhage.²⁰ Gestational age of the infants was assessed from the mother's last menstrual period, early ultrasound dating, and the new Ballard score after birth.²¹

Study Design

This study adopted the design of a prospective, double-blind, randomized, controlled model and was conducted at the NICU of the Prince of Wales Hospital, Hong Kong. Preterm, VLBW infants who were admitted consecu-

tively to the NICU and satisfied the inclusion and exclusion criteria were eligible for enrollment into the study. These infants were randomly assigned in blocks of 6 by computer-generated random numbers into the treatment group (hydrocortisone group) and the control group (placebo group), and this allocation was conducted by opening sequentially numbered sealed opaque envelopes at the pharmacy. Once the envelope was opened, the patient would be irrevocably entered into the trial. The sample size calculation was based on the NICU data in the previous 3 years. A total of 31.3% of VLBW infants who required dopamine $\geq 10 \mu\text{g}/\text{kg}$ per minute for hypotension could wean off all vasopressor support within 72 hours of starting treatment. If the percentage could be increased from 30% to 70% after treatment with a stress dose of hydrocortisone, then 24 patients would be required in each arm to achieve a statistical power of 80% ($\beta = .20$) and an α error of .05 (2-tailed) for detecting such a difference.

Drug Preparation

All medications were prepared by the pharmacy at the Prince of Wales Hospital and were sent to the NICU within 1 hour of randomization with the patient's name and randomization number attached to the syringe. Each patient received a 5-day course of treatment. VLBW infants who were randomly assigned to the hydrocortisone group received a stress dose of hydrocortisone (Solu-Cortef, hydrocortisone sodium succinate; UpJohn S.A., Puurs, Belgium) 1 mg/kg per dose every 8 hours for 5 days, and infants who were allocated to the control group received isotonic saline as placebo during the study period. The definition of the stress dose of hydrocortisone used in this study referred to the dosage that could be considered to simulate endogenous physiologic secretion of cortisol under stressful situations ($1.22 \pm 0.22 \text{ mg}/\text{kg}$ per day "physiologic" secretion of cortisol \times [3–5 times] for patients under stress).^{22,23} Hypotensive infants who required mechanical ventilation were under tremendous stress. Also, the acute situation of low BP necessitated prompt correction. Therefore, the stress dose of corticosteroids was considered appropriate as rescue treatment in this study. Although this dosage of hydrocortisone was slightly higher than that used in a recent study (hydrocortisone 2 mg/kg per day) for prophylactic treatment of hypotension,²⁴ it was lower than the high-dose dexamethasone commonly used in previous trials.^{9,10} Furthermore, the dose of hydrocortisone selected for our trial was within the range used in other studies.^{7,11,25} For ensuring effective blinding of the medications, both types of the trial drugs were colorless, odorless, and made up to the same volume before being sent to the ward. Also complying with the unit policy, all patients were commenced on intravenous prophylactic omeprazole (AstraZeneca AB, Södertälje, Sweden; 1

mg/kg intravenously, given daily for 5 days) treatment before administration of the trial medications.

Management of Systemic Hypotension in VLBW Infants

As there is no generally accepted standard of "normal" BP for preterm infants, the commonly used guidelines proposed by the Joint Working Group of the British Association of Perinatal Medicine and the Research Unit of the Royal College of Physicians (UK)¹⁹ have been adopted for use in our NICU. Hypotension is defined as a mean arterial BP lower than the numerical value of the gestational age of an infant in completed weeks.¹⁹ This definition was used in the early postnatal period throughout the study. VLBW infants who were admitted for intensive care and required regular monitoring of BP, blood gases, or hematologic and biochemical indices would receive an indwelling arterial line. It is the unit policy to retain the line until routine monitoring of vital signs and daily blood sampling have been discontinued.

Very strict guidelines were provided for attending neonatologists concerning the use of volume expanders and vasopressors for treatment of systemic hypotension in preterm infants. Three doses of fluid boluses (isotonic saline 10 mL/kg per dose) were given initially to correct presumed hypovolemia and to support the BP. Blood products such as packed cells, fresh frozen plasma, and platelets were not prescribed routinely and were used only as clinically indicated for treatment of anemia, coagulopathy, and thrombocytopenia. When volume expansion was unsuccessful in maintaining the desirable BP, vasopressors were added. Infusion of dopamine was started at a rate of 5 $\mu\text{g}/\text{kg}$ per minute, and the dose was increased in a stepwise manner by 5 $\mu\text{g}/\text{kg}$ per minute every 30 minutes until an adequate BP was achieved. The use of dobutamine was reserved for patients with poor cardiac contractility, defined as fractional shortening $< 28\%$ or ejection fraction $< 50\%$ on echocardiography, or patients whose BP was unable to be controlled by a single vasopressor. However, when 20 $\mu\text{g}/\text{kg}$ per minute dopamine and dobutamine failed to maintain an acceptable mean arterial BP, epinephrine infusion at a rate of 0.2 $\mu\text{g}/\text{kg}$ per minute was commenced. The dose was increased at a rate of 0.2 $\mu\text{g}/\text{kg}$ per minute every 30 minutes until the BP was normalized. Once the mean arterial BP had been maintained above the acceptable level for > 6 hours, weaning of vasopressors was initiated. Weaning of epinephrine was started at a rate of 0.2 $\mu\text{g}/\text{kg}$ per minute every 1 to 2 hours. Once the epinephrine infusion was discontinued, the attending neonatologist would start to decrease the infusion rate of dopamine and dobutamine, either individually or simultaneously, depending on the BP and cardiac contractility, at a rate of 5 $\mu\text{g}/\text{kg}$ per minute every 1 to 2 hours until all vasopressor support had been withdrawn. During the escalating or weaning phase of vasopressor treatment, additional doses of volume expander were administered

whenever there were indications of intravascular volume deficiency. Blood was taken for serum cortisol measurement immediately after randomization and before administration of the trial drug.

Data Collection

Data on BP measurement, use of vasopressors and volume expanders, including the average systolic, mean, and diastolic BPs in 6-hour epochs registered during the first 14 days of life; the maximum dose ($\mu\text{g}/\text{kg}$ per minute) and the cumulative dose of dopamine, dobutamine, and epinephrine ($\mu\text{g}/\text{kg}$); and the total volume of crystalloid (mL/kg) used for treatment of hypotension during the first 14 days, were calculated. The arterial BP was measured continuously through the indwelling arterial catheters in all studied infants. These data were captured by the automatic management system of the monitors, and the accuracy of the data was cross-checked manually with the clinical findings in the case records. Following our protocol in the NICU, an echocardiogram was routinely performed on all VLBW patients on day 2 or within 24 hours of completion of the prophylactic indomethacin treatment. However, additional cardiac scans would be performed as clinically indicated.

Ethical Approval

Ethical approval for the study was obtained from the Clinical Research Ethics Committee of the Chinese University of Hong Kong. The committee closely monitored any potential problem and serious adverse effects experienced by the patients during the study period. Written informed parental consent was obtained for each patient before randomization and commencement of drug treatment. The parents were allowed to withdraw their infants from the study at any time.

Statistical Analysis

The descriptive statistics were expressed as median and interquartile range or number and percentage. The Mann-Whitney U test and χ^2 test were used to compare clinical characteristics and outcomes between hypotensive infants who were treated with hydrocortisone and those who received placebo. These statistical tests were performed by SPSS for Windows (Release 11.0; SPSS Inc, Chicago, IL). The Wald statistics and an unbalance repeated measures model with first-order autoregressive covariance matrices were used to assess the trend of the mean BP between the 2 groups (BMDP/Dynamic, Release 7, Program 5V; BMDP Statistical Software Inc, Los Angeles, CA). The level of significance was set at 5% for all comparisons. The results of all randomly assigned infants were analyzed in an intention-to-treat basis.

RESULTS

The study was conducted between June 2001 and November 2004 over a 42-month period. The patient re-

cruitment process was interrupted temporarily for 6 months during the severe acute respiratory syndrome outbreak in Hong Kong. Of 143 VLBW infants who were delivered at the Prince of Wales Hospital during the study period, 48 satisfied the study criteria and were enrolled in the study. Of the recruited infants, 24 were randomly assigned to receive a stress dose of hydrocortisone, and an equal number received the placebo solution. Of the other infants ($n = 95$) who did not fulfill the criteria, 63 were not hypotensive and did not receive vasopressor treatment; 21 were mildly hypotensive and required dopamine infusion $<10 \mu\text{g}/\text{kg}$ per minute; 5 declined consent for participation into the study; 4 died shortly after birth because of multiple congenital abnormalities, hydrops fetalis, and lung hypoplasia; and 2 were commenced on systemic corticosteroids because of severe pulmonary interstitial emphysema and respiratory failure. All studied infants received surfactant for treatment of respiratory distress syndrome. Infants with necrotizing enterocolitis and intestinal perforation were reported to the Clinical Research Ethics Committee.

The clinical characteristics of the study population are summarized in Table 1. There were no significant differences between the groups in demographic and other clinical characteristics, in particular, serum cortisol concentrations immediately before randomization ($P = .55$); clinical risk index for babies score ($P = .36$); lowest systolic, mean, and diastolic BPs ($P > .47$) before randomization; and age of commencement of vasopressors ($P = .58$) and trial medications ($P = .75$).

Table 2 summarizes the clinical outcomes of the study. Nineteen (79%) compared with 8 (33%) infants in the hydrocortisone and control groups were weaned off vasopressor support within 72 hours of starting the trial drug, respectively ($P = .001$). The cumulative dose of dopamine ($P < .001$) and dobutamine ($P = .002$) after randomization in hydrocortisone-treated infants was significantly lower than in infants who received placebo. Also, significantly less volume expanders were required to support the BP ($P = .022$), and the median duration of vasopressor treatment was halved ($P = .001$) in hydrocortisone-treated infants compared with control infants (Table 2). Two and 11 infants in hydrocortisone and control groups required a second vasopressor (dobutamine and/or epinephrine; $P = .009$). In addition, the trend of the average mean arterial BP in 6-hour epochs of the 2 groups is presented in Figure 1. The trend (linear and quadratic) was significantly higher in patients who were treated with a stress dose of hydrocortisone ($P < .001$; Figure 1). In contrast, none of the major clinical or respiratory outcomes, including duration of positive pressure ventilation ($P = .63$), duration of O_2 supplementation ($P = .72$), and incidence of chronic lung disease, as defined by oxygen requirement ≥ 36 weeks postconceptional age ($P = .76$), was significantly different between the groups (Table 2). Important adverse

TABLE 1 Clinical Characteristics of the Study Population

	Hydrocortisone Group (n = 24)	Placebo Group (n = 24)	P
Gestational age, wk	27.2 (25.4–29.1)	26.0 (25.2–29.9)	.84
Birth weight, g	918 (729–1223)	920 (648–1189)	.73
Gender (female/male)	12 (50)/12 (50)	12 (50)/12 (50)	1.00
Mode of delivery (vaginal/cesarean section)	14 (58)/10 (42)	17 (71)/7 (29)	.37
Birth order (singleton/twins)	18 (75)/6 (25)	21 (88)/3 (12)	.46
Inborn/outborn	24 (100)/0 (0)	24 (100)/0 (0)	1.00
Apgar scores			
1 min	6 (5–8)	6 (5–8)	.88
5 min	8 (8–9)	8 (7–9)	.68
Arterial cord blood			
pH	7.30 (7.22–7.36)	7.29 (7.22–7.34)	1.00
Base deficit, mmol/L	–4.4 (–2.5 to –7.0)	–4.0 (–1.8 to –6.5)	.86
Cumulative dose of antenatal dexamethasone, mg	18 (8–24)	24 (6–24)	.62
Histologic chorioamnionitis	11 (46)	13 (54)	.56
Temperature on admission, °C	36 (36–37)	36 (36–36)	.45
Hematocrit on admission	0.46 (0.42–0.53)	0.50 (0.41–0.54)	.46
Prophylactic indomethacin	19 (79)	19 (79)	1.00
Echocardiographic confirmed patent ductus arteriosus	10 (42)	7 (29)	.37
Serum cortisol concentrations (immediately before randomization), nmol/L	89.0 (39.0–236.8)	110.5 (55.5–192.5)	.55
CRIB score	4 (1–7)	5 (1–9)	.36
OI (first 12 h)	5.6 (4.2–8.7)	6.9 (3.5–15.1)	.78
AaO ₂ gradient (first 12 h)	117 (88–167)	145 (78–255)	.73
Lowest systolic BP, mm Hg	29 (25–30)	29 (24–34)	.64
Lowest mean BP, mm Hg	23 (21–25)	23 (18–26)	.88
Lowest diastolic BP, mm Hg	19 (17–21)	18 (15–21)	.47
Age of commencement of vasopressor, h	5 (4–9)	7 (4–11)	.58
Age of commencement of the trial medication, h	11 (8–15)	12 (9–15)	.75

Results are median (interquartile range) or n (%). None of the clinical characteristics described in the table was significantly different between the groups. CRIB indicates clinical risk index for babies; OI, oxygenation index; AaO₂ gradient, alveolar-arterial oxygen gradient.

outcomes such as the highest serum glucose concentration ($P = .60$), culture-proven systemic infection ($P = .94$), necrotizing enterocolitis ($P = 1.00$) and intestinal perforation ($P = 1.00$), duration of hospitalization ($P = .92$), and mortality ($P = 1.00$) were similar between the 2 groups. Nonetheless, significantly more hydrocortisone-treated infants had glycosuria ($P = .029$; Table 2).

DISCUSSION

This study was started in mid-2001, and at that time, there were limited data on the effectiveness of hydrocortisone for treatment of pressor-resistant hypotension. The main source of information came from retrospective and case series studies that demonstrated a beneficial effect,^{7,10,11} but a randomized, controlled trial was unable to confirm the advantage of hydrocortisone over dopamine for treatment of hypotensive infants.²⁵ In another controlled study, high-dose dexamethasone was shown to reduce the duration of epinephrine treatment.⁹ However, there was serious concern about the harmful effects of large doses of corticosteroids on the developing brain and much controversy of using high-dose dexamethasone in preterm infants.^{26,27} Thus, the current study was specifically designed to use a relatively lower dose—the stress dose—of hydrocortisone for replacing the circulating deficient hormone and to simulate en-

dogenous cortisol release under stressful conditions. This lower dose of hydrocortisone may be a safer alternative to the high-dose dexamethasone used previously, and it also has the advantage over other synthetic corticosteroids of being metabolized directly into cortisol.

The results of the current study suggested that although circulating cortisol concentrations immediately before randomization were comparable between the groups, they represented very low levels (median serum cortisol levels: <10th centile) in infants under stress.¹⁸ Our previous study suggested that a baseline serum cortisol concentration ≤ 115 nmol/L (4.17 $\mu\text{g/dL}$) has a high specificity (91%) and positive predictive value (82%) for predicting early hypotension associated with adrenocortical insufficiency of prematurity.¹⁸ As expected with this condition, all enrolled infants were found to be hypotensive within the first 48 hours of life.^{7,10} Our assumption that $\sim 30\%$ of VLBW infants who required dopamine ≥ 10 $\mu\text{g/kg}$ per minute could wean off vasopressors 72 hours after starting treatment also corresponded closely to the clinical characteristics of control patients (8 of 24 [33%] weaned off vasopressor by 72 hours). Our findings suggested that rescue treatment with the stress dose of hydrocortisone could effectively decrease the use of volume expander, dopamine, and dobutamine for BP support. Importantly, significantly more infants were

TABLE 2 Clinical Outcomes

	Hydrocortisone Group (n = 24)	Placebo Group (n = 24)	P
Cardiovascular			
Maximum dose of dopamine, $\mu\text{g}/\text{kg}$ per min	16 (10–20)	20 (14–30)	.088
Cumulative dose of dopamine (after randomization), $\mu\text{g}/\text{kg}$	14 310 (6510–23 768)	51 875 (24 385–96 413)	<.001 ^a
Maximum dose of dobutamine, $\mu\text{g}/\text{kg}$ per min	0 (0–0)	0 (0–24)	.009 ^a
Cumulative dose of dobutamine (after randomization), $\mu\text{g}/\text{kg}$	0 (0–0)	0 (0–70 313)	.002 ^a
Maximum dose of epinephrine, $\mu\text{g}/\text{kg}$ per min	0 (0–0)	0 (0–0)	.25
Cumulative dose of epinephrine (after randomization), $\mu\text{g}/\text{kg}$ per min	0 (0–0)	0 (0–0)	.23
Infants requiring >1 vasopressor	2 (8)	11 (46)	.009 ^a
Duration of vasopressor support, h	39 (28–64)	81 (47–136)	.001 ^a
Use of volume expanders (after randomization), mL/kg	30 (0–43)	71 (30–161)	.022 ^a
Respiratory			
Duration of IPPV/HFOV, d	10 (3–44)	15 (3–30)	.92
Duration of positive pressure ventilation (including CPAP), d	37 (8–78)	43 (9–58)	.63
Duration of O ₂ supplementation, d	19 (2–58)	20 (3–40)	.72
Maximum Fio ₂	0.5 (0.4–1.0)	0.5 (0.4–0.8)	.77
Maximum mean airway pressure, cm H ₂ O	11.1 (8.7–13.4)	11.2 (8.6–13.8)	.75
O ₂ requirement at 36 wk postconceptional age	9 (38)	8 (33)	.76
Use of postnatal dexamethasone	6 (25)	7 (29)	.75
Pulmonary interstitial emphysema	3 (12.5)	3 (12.5)	1.00
Pulmonary hemorrhage	1 (4)	2 (8)	1.00
Pneumothorax	2 (8)	1 (4)	1.00
Others			
Highest serum glucose concentrations, mmol/L	10.7 (7.8–16.5)	11.0 (8.0–12.7)	.60
Glycosuria	11 (46)	4 (17)	.029 ^a
Intraventricular hemorrhage \geq grade 3	3 (13)	5 (21)	.70
Periventricular leukomalacia	1 (4)	1 (4)	1.0
Necrotizing enterocolitis	2 (8)	3 (12.5)	1.0
Gastric aspirates			
green (bile-stained)	8 (34)	9 (38)	.81
brown (coffee ground)	2 (8)	3 (12)	
normal	14 (58)	12 (50)	
Gastrointestinal perforation	1 (4)	2 (8)	1.00
Age achieved full enteral feeding, d	36 (19–50)	28 (18–49)	.82
Culture proven sepsis (episodes/patient)	1 (0–1)	0 (0–2)	.94
Retinopathy of prematurity \geq stage III	1 (4)	2 (8)	1.00
Duration of hospitalization, d	105 (51–140)	111 (53–142)	.92
Died	4 (17)	3 (12.5)	1.0

Results are median (interquartile range) or n (%). IPPV indicates intermittent positive pressure ventilation; HFOV, high-frequency oscillatory ventilation; CPAP, continuous positive airway pressure; Fio₂, fractional inspired O₂ concentration.

^a Statistically significant results.

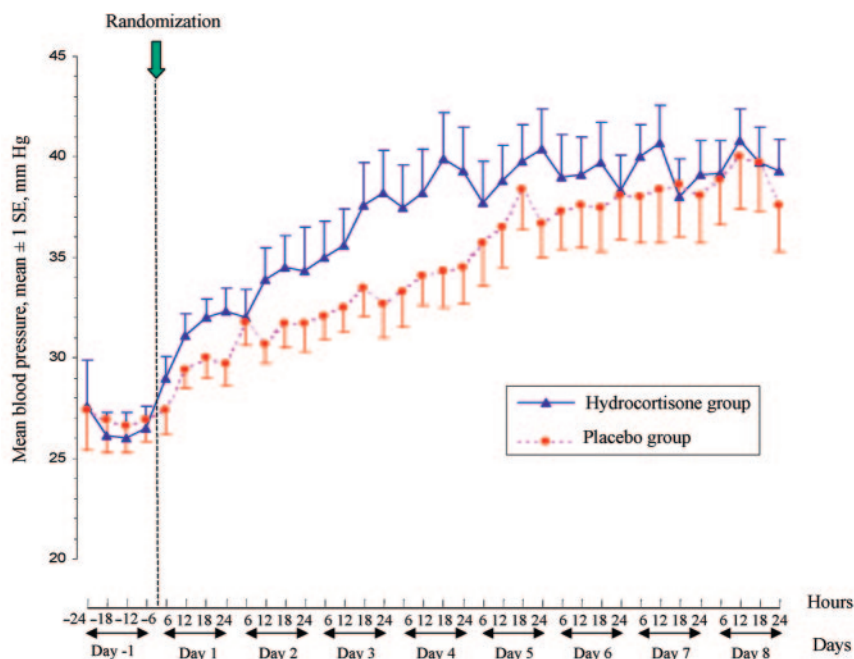
weaned off vasopressors support 72 hours after commencement of hydrocortisone. The median duration of vasopressor treatment was halved, and significantly fewer VLBW infants required a second vasopressor in the hydrocortisone group (Table 2). Similar to the observations in previous studies,^{28,29} the BP of VLBW infants in both study groups increased progressively with postnatal age (Figure 1). The trend of the mean arterial BP was significantly and consistently higher in infants who received the stress dose of hydrocortisone compared with control patients (Figure 1). Thus, we have demonstrated that a lower dose of corticosteroid was likely to be as effective as the high-dose dexamethasone^{8–10} commonly used for treatment of refractory hypotension. As it is well documented that systemic corticosteroids may have many short- and long-term adverse effects,^{26,27,30,31} the lowest effective dose should be rec-

ommended for clinical use when emergency and life-threatening situations arise.^{32,33} Also similar to our findings, a recent controlled study indicated that prophylactic treatment with hydrocortisone decreased the incidence of hypotension, as defined by the need for vasopressor treatment, among extremely low birth weight infants during the first 2 days of life.²⁴ The investigators found that 7% of infants in the hydrocortisone group versus 39% in the placebo group required vasopressor support on the second day of life.²⁴ As the current study was not intended or designed to assess the clinical outcomes, it therefore was not unexpected to find that major clinical outcomes were similar between the groups (Table 2).

The mechanisms by which corticosteroids facilitate an improvement in systemic BP are not completely understood. It has been shown that the cardiovascular adren-

FIGURE 1

The trend of the average mean arterial BP (mean \pm SE) in 6-hour epochs between the hydrocortisone and the placebo groups. The trend (linear and quadratic) of the mean arterial BP after randomization was significantly higher in infants who received a stress dose of hydrocortisone compared with those who received placebo ($P < .001$).



ergic receptors and components of the second messenger systems are inducible by corticosteroids.¹¹ Exposure to this class of drugs can increase the expression and density of β adrenergic receptors within a few hours via a genomic effect.^{34,35} Corticosteroids can also reverse the desensitization effect of prolonged catecholamine exposure on the receptors^{34,36} and increase the expression of the angiotensin 2 (type 1) receptor gene of the myocardium.³⁷ These actions may enhance both cardiac muscle and vascular smooth muscle responsiveness to endogenous and exogenous catecholamines, resulting in a rapid upsurge of systemic BP. In addition, corticosteroids have mineralocorticoid action, which can promote an additional increase in BP.

Although the objective of this study primarily was to assess the effectiveness of a stress dose of hydrocortisone for treatment of refractory hypotension, serious short- and medium-term side effects were monitored. One and 2 patients in the hydrocortisone and control groups, respectively, had intestinal perforation. All of these patients were proved to have necrotizing enterocolitis radiologically and histologically, and 1 in each group was also documented to have absent end-diastolic flow on antenatal Doppler assessment. In all cases, the bowel perforation occurred after hydrocortisone and omeprazole treatment had been discontinued. A total of 79.2% of patients in the cohort received prophylactic indomethacin. Whether the absence of spontaneous intestinal perforation was a coincidental finding, related to the relatively short course of hydrocortisone used in this study or associated with the routine and prophylactic use of omeprazole in all infants who were commenced on systemic corticosteroids, remains undetermined. Pro-

ton pump inhibitors can decrease gastric acid production and facilitate mucosal healing, thereby conferring protection to the mucosa against perforation. However, the relatively small sample size of the study would not have adequate statistical power to detect such a small difference, and a larger randomized, controlled study is required to delineate the protective effect of this class of drugs in the future. Furthermore, the incidence of infants with greenish and coffee-ground aspirates were similar between the 2 groups. Other important side effects of systemic corticosteroids, including systemic bacterial or fungal infection, intracranial hemorrhage, and periventricular leukomalacia, were not increased in hydrocortisone-treated infants. Although serum glucose concentrations were comparable between the groups, significantly more infants who were treated with hydrocortisone had glycosuria.

CONCLUSION

Our findings suggested that a stress dose of hydrocortisone was effective in treating infants with refractory hypotension. These patients were likely to have adrenocortical insufficiency of prematurity as evidenced by their very low circulating cortisol concentrations at the time of hypotension and severe stress. Treated infants required significantly less volume expander, dopamine, and dobutamine to maintain an acceptable BP. More important, the duration of vasopressor treatment was significantly reduced, and fewer patients required a second vasopressor. Although this study demonstrated that a stress dose of hydrocortisone was effective for treatment of early refractory hypotension, it could not be recommended for prophylaxis or routine clinical use

because of its potential serious adverse effects,^{26,27,30,31} and only a proportion of VLBW infants with adrenocortical insufficiency would benefit from the treatment.^{6–11,18} Because the recent controlled study on chronic lung disease did not observe a significant decrease in body and brain growth associated with the use of hydrocortisone,³⁸ systemic corticosteroids with the lowest effective dose therefore should be used in preference to high-dose dexamethasone in emergency and life-threatening situations, especially when perfusion to vital organs is being compromised. However, the concomitant use of systemic corticosteroids with indomethacin remains a major hazard in early postnatal life.^{30,31} The prophylactic use of proton pump inhibitors for prevention of spontaneous gastrointestinal perforation warrants additional exploration. Future randomized, controlled studies should focus on evaluating important clinical outcomes associated with the use of the stress dose of hydrocortisone for treatment of early refractory hypotension and adrenocortical insufficiency of prematurity.

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A Double-Blind, Randomized, Controlled Study of a "Stress Dose" of Hydrocortisone for Rescue Treatment of Refractory Hypotension in Preterm Infants

Pak C. Ng, Cheuk H. Lee, Flora Liu Bnur, Iris H.S. Chan, Anthony W.Y. Lee, Eric Wong, Hin B. Chan, Christopher W.K. Lam, Benjamin S.C. Lee and Tai F. Fok

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