Postoperative Hydrocortisone Infusion Reduces the Prevalence of Low Cardiac Output Syndrome After Neonatal Cardiopulmonary Bypass*

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Objective: Neonatal cardiac surgery with cardiopulmonary bypass is often complicated by morbidity associated with inflammation and low cardiac output syndrome. Hydrocortisone "stress dosing" is reported to provide hemodynamic benefits in some patients with refractory shock. Development of cardiopulmonary bypass-induced adrenal insufficiency may provide further rationale for postoperative hydrocortisone administration. We sought to determine whether prophylactic, postoperative hydrocortisone infusion could decrease prevalence of low cardiac output syndrome after neonatal cardiac surgery with cardiopulmonary bypass.

Design: Double-blind, randomized control trial.

Setting: Pediatric cardiac ICU and operating room in tertiary care center.

Patients: Forty neonates undergoing cardiac surgery with cardiopulmonary bypass were randomized (19 hydrocortisone and 21 placebo). Demographics and known risk factors were similar between groups.

Interventions: After cardiopulmonary bypass separation, bolus hydrocortisone (50 mg/m²) or placebo was administered, followed by continuous hydrocortisone infusion (50 mg/m²/d) or placebo tapered over 5 days. Adrenocorticotropic hormone stimulation testing (1 µg) was performed before and after cardiopulmonary bypass, prior to steroid administration. Blood was collected for cytokine analysis before and after cardiopulmonary bypass.

Measurements and Main Results: Subjects receiving hydrocortisone were less likely to develop low cardiac output syndrome (5/19, 26% vs 12/21, 57%; p = 0.049). Hydrocortisone group had more negative net fluid balance at 48 hours (−114 vs −64 mL/kg; p = 0.01) and greater urine output at 0–24 hours (2.7 vs 1.2 mL/kg/hr; p = 0.03). Hydrocortisone group weaned off catecholamines and vasopressin sooner than placebo, with a difference in inotrope-free subjects apparent after 48 hours (p = 0.033). Five placebo subjects (24%) compared with no hydrocortisone subjects required rescue steroids (p = 0.02). Thirteen (32.5%) had adrenal insufficiency after cardiopulmonary bypass. Patients with adrenal insufficiency randomized to receive hydrocortisone had lower prevalence of low cardiac output syndrome compared with patients with adrenal insufficiency randomized to placebo (1/6 vs 6/7, respectively; p = 0.02). Hydrocortisone significantly reduced proinflammatory cytokines. Ventilator-free days, hospital length of stay, and kidney injury were similar.

Conclusions: Prophylactic, postoperative hydrocortisone reduces low cardiac output syndrome, improves fluid balance and urine output, and attenuates inflammation after neonatal cardiopulmonary bypass surgery. Further studies are necessary to show if these benefits lead to improvements in more important clinical outcomes. (Pediatr Crit Care Med 2015; 16:629–636)

Key Words: adrenal insufficiency; cardiopulmonary bypass; congenital heart disease; hydrocortisone; inflammation; low cardiac output syndrome

Cardiopulmonary bypass (CPB) is associated with significant morbidity related to systemic inflammation and low cardiac output syndrome (LCOS) (1, 2). Neonates often have an exaggerated inflammatory response and may be at higher risk for the deleterious effects of CPB (3). In an attempt to reduce morbidity from inflammation, most centers use perioperative steroids (4). Numerous studies have shown that perioperative steroids blunt the proinflammatory cytokine response to CPB (5–8), but data conflict on whether steroids are associated with improved clinical outcomes (9). Despite the lack of conclusive evidence, an international survey of pediatric cardiac intensive care society members revealed that the majority of centers use perioperative steroids in selected patients, 40% use them routinely in all cases,
and 22% of centers continue steroid administration postoperatively (4).

LCOS occurs frequently after neonatal bypass, and “stress dose” hydrocortisone has been reported to confer hemodynamic benefits in neonates requiring high levels of inotropic support (10). Benefits of postoperative steroids may result from suppression of inflammatory cytokines or direct actions on the heart and vascular smooth muscle. A third explanation for hemodynamic improvement after steroids is the existence of a subgroup with adrenal insufficiency (AI). A number of studies suggest that CPB may actually induce AI (11, 12), that neonates are particularly vulnerable to AI, and that AI contributes to postoperative morbidity and mortality (13–15).

This double-blinded, randomized, placebo-controlled trial was designed to determine if prophylactic hydrocortisone infusion in the immediate postoperative period could decrease the development of LCOS. We further sought to determine the prevalence of AI in our population and to determine the impact of hydrocortisone infusion post-CPB inflammation and other clinical outcomes in neonates with and without AI.

MATERIALS AND METHODS

Subjects

The institutional review board at the University of Alabama at Birmingham approved this study. Written, informed consent was obtained. Infants undergoing surgical repairs typically performed in the neonatal period that required CPB were eligible for enrollment. Those who failed to separate from CPB were excluded. Thirty-eight neonates and two infants (ages 35 and 43 d old) were enrolled from June 2012 to November 2013.

Endpoints and Definitions

The primary outcome was death or development of LCOS in the first postoperative 48 hours. LCOS was defined as age-specific tachycardia, hypotension, central venous desaturation, or oliguria leading to cardiac arrest, doubling or adding a new inotrope, or extracorporeal membrane oxygenation (ECMO) (16). Secondary clinical outcomes included postoperative duration of mechanical ventilation, ventilator-free days, postoperative ICU length of stay (LOS), postoperative hospital LOS, in-hospital mortality, and development of acute kidney injury (AKI), where AKI was defined as doubling of the preoperative serum creatinine. Modified inotrope score (IS) was used to reflect frequent use of vasopressor (17). Milrinone was not included in the IS calculation because of ubiquitous use. Elevated blood glucose (>180 mg/dL) and nosocomial infections (positive culture with clinical diagnosis of infection) were reported as adverse events potentially related to hydrocortisone. Laboratory values and vital signs related to cardiac output and oxygen transport were also prospectively collected.

Study Protocol

Subjects were randomized in 1:1 fashion to either IV hydrocortisone succinate or placebo and were stratified by procedure type by a nonblinded study pharmacist. Hydrocortisone (50 mg/m²) was initiated as a bolus in the operating room after removal of CPB and after adrenocorticotropic hormone (ACTH) stimulation testing. A continuous infusion of hydrocortisone (50 mg/m²/d) began immediately after the loading dose. Subjects randomized to placebo received 0.9% saline in equal volume instead. A nonblinded study pharmacist stratified cases by surgical procedure to achieve a balance between study arms with respect to Norwood procedure and arterial switch operation. The infusion was continued for 48 hours and then tapered over 3 days as follows: 40 mg/m²/d × 24 hours, 30 mg/m²/d × 12 hours, 20 mg/m²/d × 12 hours, 10 mg/m²/d × 24 hours, then stop. For placebo subjects, an infusion of 0.9% saline was titrated at isovolumetric rate to hydrocortisone infusion and tapered identically by volume. The multidisciplinary clinical team directed all other clinical care.

Preoperative and Intraoperative Management

At 8 hours and 1 hour prior to their operations, all subjects received methylprednisolone (10 mg/kg). None received intraoperative steroids or etomidate. CPB circuit prime consisted of 25% albumin, fresh-frozen plasma (20 mL/kg), packed RBCs, mannitol, sodium bicarbonate, and Normosol-R. Patients underwent zero-balance ultrafiltration during CPB and single-pass ultrafiltration afterward. Those requiring aortic cross clamp were cooled to 22°C and received one dose of DelNido cardioplegia. During arch reconstruction, continuous low-flow cerebral perfusion was employed.

Postoperative Management

Subjects were managed postoperatively according to our routine clinical protocols targeting age- and lesion-specific variables. All subjects arrived to the ICU on milrinone 0.5 μg/kg/min with or without epinephrine and/or vasopressin infusions. At the discretion of the attending physician, rescue steroids (50 mg/m² hydrocortisone IV bolus) could be given for severe, catecholamine-resistant shock. If clinical improvement and decreased catecholamine requirement occurred within the first 4 hours after rescue steroid dosing, steroids were continued at 50 mg/m²/d divided every 6 hours without discontinuation of the study infusion. Peritoneal dialysis (PD) was started on all subjects within 6 hours after arrival to the ICU (18). Cerebral and renal near-infrared spectroscopy (NIRS) were used on all patients through extubation.

Adrenal Function Testing

Subjects underwent two ACTH stimulation tests: the first occurring before preoperative steroids and the second after CPB. Serum cortisol was measured before and 30 minutes after 1 μg cosyntropin (19); results were not available to the clinical team. AI was defined as an increase in cortisol of less than 9 μg/dL from baseline (20).

Cytokine Sampling and Analysis

Whole blood was obtained for cytokine analysis preoperatively and at 0, 4, 12, 24, and 48 hours after CPB. Samples were processed at the time of collection and stored at –80°C. Samples were analyzed in duplicate using a multiplex
Electrochemiluminescence detection method (MSD 2400 imager; Meso Scale Diagnostics, Gaithersburg, MD).

**Statistical Analysis**

Analysis was performed by intention-to-treat. Continuous variables not normally distributed were summarized as a median with interquartile range (IQR), with group comparison performed using the Mann-Whitney test. Continuous variables with a normal distribution were summarized as means with SD and compared using the unpaired Student t test. Categorical data were compared using chi-square or Fisher exact test as indicated. p values of less than 0.05 were considered statistically significant. All statistical tests were two-tailed. SPSS version 22 (IBM, Chicago, IL) was used for all statistical analysis. Study sample size was powered to detect a 60% difference in LCOS between groups at α 0.05 and β 0.70, assuming the prevalence of LCOS after neonatal bypass of 65% (based on retrospective data of patients who died, required rescue steroids, ECMO, or epinephrine > 0.1 μg/kg/min).

**RESULTS**

**Subjects and Demographics**

Of the 57 patients who were eligible for inclusion during the study period, 44 consented. One patient died before the operation, and one patient did not require CPB. Of the 42 subjects randomized, two were excluded due to failure to separate from CPB. Forty subjects received the study drug (19 hydrocortisone and 21 placebo). The study groups were similar with respect to basic demographics, surgical complexity, and pre- and intraoperative risk factors (Table 1).

LCOS, Oxygen Delivery, and Hemodynamic Variables

LCOS developed in 17 subjects (42.5%), occurring at median 7 hours (IQR, 6, 11) after CPB. Subjects receiving HC were less likely to develop LCOS than those receiving placebo (26% vs 57%; p = 0.049). Arteriovenous oxygen and Cox differences at ICU admission were both lower in the hydrocortisone group compared with placebo (Table 2). The median time from hydrocortisone bolus to ICU admission was 99 minutes (IQR, 62, 135). Serum lactate at 12 and 24 hours were not significantly different between groups. Although median lactate concentration was significantly lower in placebo at 48 hours, this difference was not clinically important, as the lactate concentration had normalized in both groups by this time. Median IS was not different between groups at 12, 24, or 48 hours. However, Kaplan-Meier analysis showed that hydrocortisone group reached IS zero faster than placebo (p = 0.03) (Fig. 1). In the first 48 postoperative hours, a blinded clinical attending physician deemed five placebo subjects (24%) to require “rescue steroids” due to fluid- and catecholamine-refractory shock versus none in the hydrocortisone arm (p = 0.02). Mean heart rate, temperature, central venous pressure, and cerebral and renal NIRS were not different between groups in the first or second 24-hour time periods after ICU admission (Table 3). Average mean arterial pressure from 25 to 48 hours was higher in the hydrocortisone group. Two placebo subjects and one hydrocortisone subject required ECMO.

**Clinical Outcomes**

Clinical outcomes are shown in Table 4. Urine output (UOP) in the first 24 hours was significantly higher in the hydrocortisone group (2.7 mL/kg/hr [IQR, 0.9, 3.4] vs 1.2 mL/kg/hr [IQR, 0.9, 1.6]).

<table>
<thead>
<tr>
<th>TABLE 1. Demographic Characteristics: Preoperative and Operative Exposures of Randomized Patients</th>
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</thead>
<tbody>
<tr>
<td>Variable</td>
</tr>
<tr>
<td>Age at operation, d</td>
</tr>
<tr>
<td>Gestational age, wk</td>
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<tr>
<td>Weight, kg</td>
</tr>
<tr>
<td>Surgical procedure, n (%)</td>
</tr>
<tr>
<td>Norwood</td>
</tr>
<tr>
<td>Arterial switch operation</td>
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<tr>
<td>Interrupted aortic arch repair</td>
</tr>
<tr>
<td>Aortic arch augmentation</td>
</tr>
<tr>
<td>Truncus arteriosus repair</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Preoperative intubation, n (%)</td>
</tr>
<tr>
<td>Cardiopulmonary bypass, min</td>
</tr>
<tr>
<td>Aortic cross clamp time, min</td>
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<tr>
<td>Delayed sternal closure, n (%)</td>
</tr>
</tbody>
</table>

IQR = interquartile range.
At 48 hours, fluid balance was 78% more negative in the hydrocortisone group than the placebo group (–114 [IQR, –148, –60] vs –64 [IQR, –107, 12]; p = 0.04). Overall mortality was 7.5% (3/40), confined to the placebo group. Ventilator-free days, total length of mechanical ventilation, ICU LOS, and hospital LOS were not significantly different between groups. Seven subjects in each group (hydrocortisone 37% and placebo 33%) developed AKI.

Baseline Cortisol and ACTH Stimulation Testing
Preoperative median random serum cortisol was 13.3 μg/dL (IQR, 7.9, 36.2). Immediately after CPB, the median random cortisol increased to 70.1 μg/dL (IQR, 42.8, 131.3; p < 0.001). Two subjects (5%) met criteria for AI preoperatively; 13 (32.5%) had AI after CPB (p = 0.004). Fifty-four percent of postoperative AI subjects (7/13) developed LCOS compared with 37% (10/27) among those without AI (p = 0.51). Subjects with postoperative AI randomized to hydrocortisone were less likely to develop LCOS than subjects with AI who received placebo (17% [1/6] vs 86% [6/7], respectively; p = 0.02).

Cytokines
Figure 2 demonstrates serum cytokine concentrations at six time points. Preoperative and time-zero cytokine concentration were not different between the treatment arms; however, 12, 24, and 48 hours after CPB, interleukin (IL)-6, and tumor necrosis factor-α were significantly lower in subjects receiving hydrocortisone (p < 0.01). IL-1β and IL-8 were significantly lower in the hydrocortisone group at 24 and 48 hours but not at 12 hours (p < 0.05). The anti-inflammatory cytokine IL-10 concentration was higher in the hydrocortisone group at 4 hours (p = 0.03).
Adverse Events
Mean glucose (hydrocortisone, 119 mg/dL vs placebo, 130 mg/dL; 
p = 0.4) and prevalence of at least one episode of hyperglycemia (hydrocortisone 68% vs placebo 81%; p = 0.47) were not different between groups. Three placebo subjects and one hydrocortisone subject required insulin. There were no documented episodes of hypoglycemia in either group. There were no episodes of clinically significant gastrointestinal bleeding or perforation. Fifteen subjects received antibiotics for a suspected infection (7/19 in the hydrocortisone and 8/21 in the placebo group). Four subjects had positive cultures: two positive tracheal aspirates in placebo group (Candida and gamma-hemolytic Streptococcus) and two positive blood cultures in hydrocortisone group (Staphylococcus epidermidis and Klebsiella pneumoniae). Although all four subjects were treated for clinical infection, only the Klebsiella bacteremia met Centers for Disease Control and Prevention criteria for hospital-acquired infection.

DISCUSSION
In this double-blinded, randomized, controlled trial of postoperative hydrocortisone versus placebo, we showed greater than 50% reduction in the prevalence of LCOS in subjects treated with prophylactic hydrocortisone infusion after neonatal CPB. Hydrocortisone infusion was also associated with improved UOP, more negative fluid balance at 48 hours, and a reduction in proinflammatory cytokines without increased prevalence of hyperglycemia or infection. In addition, we demonstrate that cardiac surgery with CPB may induce AI as determined by ACTH stimulation assays. This study adds to a growing body

### TABLE 3. Secondary Outcomes and Adverse Events

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hydrocortisone (n = 19)</th>
<th>Placebo (n = 21)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate 0–24 hr, beats/min</td>
<td>159 ± 18</td>
<td>165 ± 13</td>
<td>0.23</td>
</tr>
<tr>
<td>Heart rate 25–48 hr, beats/min</td>
<td>152 ± 16</td>
<td>160 ± 18</td>
<td>0.14</td>
</tr>
<tr>
<td>MAP 0–24 hr, mm Hg</td>
<td>55 ± 9</td>
<td>56 ± 11</td>
<td>0.76</td>
</tr>
<tr>
<td>MAP 25–48 hr, mm Hg</td>
<td>64 ± 9</td>
<td>56 ± 8</td>
<td>0.01</td>
</tr>
<tr>
<td>CVP 24 hr, 0–24 hr, mm Hg</td>
<td>11 ± 3</td>
<td>11 ± 5</td>
<td>1.00</td>
</tr>
<tr>
<td>CVP 48 hr, 25–48 hr, mm Hg</td>
<td>10 ± 4</td>
<td>8.5 ± 6</td>
<td>0.36</td>
</tr>
<tr>
<td>cNIRS 0–24 hr, %</td>
<td>73 ± 11</td>
<td>69 ± 10</td>
<td>0.24</td>
</tr>
<tr>
<td>cNIRS 25–48 hr, %</td>
<td>66 ± 9</td>
<td>62 ± 10</td>
<td>0.21</td>
</tr>
<tr>
<td>rNIRS 0–24 hr, %</td>
<td>73 ± 10</td>
<td>68 ± 8</td>
<td>0.09</td>
</tr>
<tr>
<td>rNIRS 25–48 hr, %</td>
<td>69 ± 9</td>
<td>64 ± 8</td>
<td>0.07</td>
</tr>
<tr>
<td>Temperature 0–24 hr, °C</td>
<td>36.6 ± 0.4</td>
<td>36.6 ± 0.7</td>
<td>1.00</td>
</tr>
<tr>
<td>Temperature 25–48 hr, °C</td>
<td>36.8 ± 0.5</td>
<td>36.8 ± 0.7</td>
<td>1.00</td>
</tr>
</tbody>
</table>

MAP = mean arterial pressure, CVP = central venous pressure, cNIRS = cerebral near-infrared spectroscopy, rNIRS = renal near-infrared spectroscopy. All data are presented as mean with sd.

### TABLE 4. Clinical Outcomes

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hydrocortisone (n = 19)</th>
<th>Placebo (n = 21)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality, n (%)</td>
<td>0 (0)</td>
<td>3 (14)</td>
<td>0.23</td>
</tr>
<tr>
<td>Urine output 0–24 hr, mL/kg/hr</td>
<td>2.7 (IQR, 1, 3.4)</td>
<td>1.2 (IQR, 0.7, 1.5)</td>
<td>0.03</td>
</tr>
<tr>
<td>48-hr fluid balance, mL/kg</td>
<td>−114 (IQR, −148, −60)</td>
<td>−64 (IQR, −107, 12)</td>
<td>0.04</td>
</tr>
<tr>
<td>Time until first extubation, hr</td>
<td>51 (IQR, 34, 83)</td>
<td>55 (IQR, 21, 195)</td>
<td>0.7</td>
</tr>
<tr>
<td>Acute kidney injury, n (%)</td>
<td>7 (37)</td>
<td>7 (33)</td>
<td>1</td>
</tr>
<tr>
<td>ICU LOS, hr*</td>
<td>213 (IQR, 118, 501)</td>
<td>162 (IQR, 137, 389)</td>
<td>0.76</td>
</tr>
<tr>
<td>Hospital LOS, da*</td>
<td>19 (IQR, 9, 24)</td>
<td>13.5 (IQR, 9, 24)</td>
<td>0.62</td>
</tr>
<tr>
<td>Blood glucose &gt; 180 mg/dL, n (%)</td>
<td>10 (53)</td>
<td>15 (71)</td>
<td>0.3</td>
</tr>
<tr>
<td>Antibiotics for suspected infection, n (%)</td>
<td>7 (37)</td>
<td>8 (38)</td>
<td>1</td>
</tr>
</tbody>
</table>

IQR = interquartile range, LOS = length of stay. *Excluding three patients who died.

Adverse Events
Mean glucose (hydrocortisone, 119 mg/dL vs placebo, 130 mg/dL; 
p = 0.4) and prevalence of at least one episode of hyperglycemia (hydrocortisone 68% vs placebo 81%; p = 0.47) were not different between groups. Three placebo subjects and one hydrocortisone subject required insulin. There were no documented episodes of hypoglycemia in either group. There were no episodes of clinically significant gastrointestinal bleeding or perforation. Fifteen subjects received antibiotics for a suspected infection (7/19 in the hydrocortisone and 8/21 in the placebo group). Four subjects had positive cultures: two positive tracheal aspirates in placebo group (Candida and gamma-hemolytic Streptococcus) and two positive blood cultures in hydrocortisone group (Staphylococcus epidermidis and Klebsiella pneumoniae). Although all four subjects were treated for clinical infection, only the Klebsiella bacteremia met Centers for Disease Control and Prevention criteria for hospital-acquired infection.
of literature pertaining to the impact of steroid administration after neonatal cardiac surgery and, in particular, to potential benefits for CPB-induced adrenal dysfunction and LCOS.

LCOS is common after cardiac surgery due to CPB-related inflammation, residual lesions, hypothermia, myocardial ischemia/reperfusion injury, and the effects of ventriculotomy (21). In our trial, LCOS occurred in 43% of all patients and more frequently in those who did not receive hydrocortisone. Between 6 and 12 hours after neonatal CPB, a reversible reduction in cardiac output by up to 30% often occurs. In this vulnerable time period, further metabolic demands may lead to hypoperfusion, lactic acidosis, and organ injury. Exogenous steroid administration has been one strategy to treat or prevent CPB-induced LCOS, but with unproven benefit. Steroids have numerous beneficial effects on cardiac function and vasomotor tone, increasing adrenergic receptor density, reducing pathologic vasodilation, and increasing bioavailable calcium (22, 23). They potentiate the effects of catecholamines and angiotensin II on vascular smooth muscle and decrease capillary leak (24–27). Steroids may improve cardiac output and reduce inflammation after cardiac surgery, lowering heart rate, increasing blood pressure, and reducing the duration of requirement for epinephrine (28–30). Only one small, prospective study has evaluated the use of prophylactic steroids in the postoperative period: Ando et al evaluated 20 neonates after biventricular repair and showed hydrocortisone was associated with decreased fluid accumulation and improved respiratory outcomes (31). In our prior retrospective review, we showed that 40% of neonates with LCOS after cardiac surgery with CPB responded to rescue steroids with improved hemodynamics (32).

Hypothalamic-pituitary-adrenal (HPA) axis dysfunction may further contribute to the development of LCOS, providing further rationale for supplementation with steroids. Both ACTH and cortisol fall in infants after heart surgery, and elevation of ACTH/cortisol ratio has been associated with increased need for inotropic support (11, 12, 33, 34). Some studies suggest that AI is common after neonatal cardiac surgery with CPB, occurring in up to 47% of subjects (31, 33–36). One third of subjects in our trial developed AI after CPB; in fact, we provide the first evidence that post-CPB ACTH nonresponsiveness may develop in patients who had normal response in the immediate preoperative period. The decreased prevalence of LCOS in the hydrocortisone group was not consistently linked to the cortisol response to ACTH. Notably, however, almost all AI subjects randomized to placebo developed LCOS, while almost all AI subjects randomized to preemptive hydrocortisone did not.
Although underpowered, these data suggest that preemptive hydrocortisone may protect some neonates with postoperative AI from developing hemodynamic compromise. Others have failed to demonstrate any association between HPA dysfunction and prevalence of LCOS and inotrope requirement; however, these investigators used much higher doses of cosyntropin (125 µg) than the present study (11, 34). We speculate that a low-dose stimulation test has greater sensitivity to impairments in adrenal function and thus better predicts responsiveness to steroids as opposed to larger doses of cosyntropin, which may identify only the most severe cases of adrenal dysfunction. The fact that some subjects with AI did not develop LCOS underscores the multifactorial nature of LCOS after cardiac surgery. Likewise, that hydrocortisone produced hemodynamic improvements in some patients without AI suggests that postoperative steroids may have a role beyond correction of “cortisol deficiency.”

CPB induces an exaggerated systemic inflammatory response in neonates that may lead to significant morbidity (1, 3, 37–40). Like many previous investigators, we show that hydrocortisone significantly decreases proinflammatory cytokines after neonatal CPB (30). It must be noted that all patients in our trial received preoperative steroids, which have also been shown to decrease post-CPB inflammation (5–8). Although we cannot comment about the impact of preoperative steroids in our trial, we can conclude that the addition of postoperative hydrocortisone infusion to our preoperative steroid regimen significantly attenuates the post-CPB proinflammatory response. Elevation in postoperative proinflammatory cytokine concentration has been correlated with greater need for inotropic support, lower central venous saturation, higher lactate, prolonged ventilation, increased peritoneal drainage, and longer ICU LOS in children after cardiac surgery with CPB (39). In patients with hypoplastic left heart syndrome, increased IL-6 was found to be associated with mortality (38). Nevertheless, there is inadequate evidence to suggest that suppression of the cytokine response improves clinical outcomes. Our finding that subjects receiving hydrocortisone had improved outcomes in conjunction with reduced serum cytokines suggests this, but multiple confounders make our trial underpowered to assign an independent causative relationship between hydrocortisone-induced cytokine amelioration and outcome per se.

Subjects receiving hydrocortisone also attained more negative fluid balance at 48 hours and over twice the UOP at 24 hours. This may have been due to improvements in hemodynamics and/or capillary leak, enabling fewer colloid boluses and allowing them to sustain more aggressive fluid removal via PD. This study was not powered to detect differences in any of the secondary, important clinical outcomes (duration of mechanical ventilation, LOS, mortality, etc.), and no other differences were seen. Vital signs were similar, albeit with a consistent trend toward lower heart rate, higher mean arterial pressure, and higher renal NIRS in the hydrocortisone group. Due to our use of strict ICU protocols aimed at attaining lesion-specific hemodynamic variables, comparisons of vital signs as surrogates of cardiac output may be unhelpful. Pharmacologic support needed to achieve these hemodynamic variables, however, was different between groups. The placebo group had a significantly longer duration of inotropic support, and 24% of placebo subjects were diagnosed with refractory shock (subsequently receiving rescue steroid boluses) versus none for those assigned to receive hydrocortisone.

Insulin resistance is a known side effect of steroids. However, in our study, the hydrocortisone group did not have a higher prevalence of hyperglycemia compared with the placebo group. Likewise, the prevalences of infection and gastrointestinal side effects were not different between groups. Use of postoperative steroids in each treatment arm and availability of rescue steroids to placebo subjects together make interpretation of possible adverse effects of postoperative steroids challenging. In any case, this pilot study was not powered to assess adverse effects of steroids in the ICU or their long-term effects on neurodevelopment. Thus conclusions about safety must ultimately await a larger study.

This study has a number of limitations, the most important of which is heterogeneous, single-center trials. We used the prevalence of LCOS as the primary outcome variable. Although this outcome may be adequate to show efficacy in this small, pilot study, improvements in more clinically important outcomes should be established in a large, multicenter trial before postoperative steroid prophylaxis is broadly recommended. We included subjects from more than one surgeon, and doing so may have introduced uncontrolled variability. All of our patients received preoperative methylprednisolone, and rescue hydrocortisone was permissible within both arms of the study. There is therefore no comparison made between “steroids” and “no steroids.” Rather, the comparison is between a postoperative hydrocortisone infusion and a placebo infusion.

Methylprednisolone is known to cross-react with cortisol assays. We assume that since all patients received methylprednisolone, the effects on stimulation assays will be uniform throughout the study, but recognize this assumption as such.

The expected effect of our allowance for rescue hydrocortisone in placebo subjects, if any, would be to diminish the detectability of a treatment effect. That such an effect was nonetheless detectable is noteworthy. Furthermore, allowing rescue hydrocortisone provided the opportunity to analyze “need for rescue” among secondary outcome variables. And although blinded clinicians were permitted to provide rescue steroids according to their own subjective criteria, we find their frequent decision to do so among placebo subjects but not among hydrocortisone subjects to be further evidence in support of our hypothesis.

Some authors recommend differentiation between free and total cortisol in evaluating AI. We suspect this distinction is unnecessary when evaluating AI using ACTH stimulation assays (vs random cortisol) and therefore measured only total cortisol. We used a low-dose (1 µg) ACTH stimulation test. Although a precedent for such dosing exists in neonates after cardiac surgery, adult recommendations for diagnosing AI in critical illness call for 0.5–1 µg. Perhaps, an even lower dose should be used in neonates (20).
CONCLUSIONS
We conclude that prophylactic hydrocortisone infusion in the postoperative period reduces the prevalence of LCOS in neonates after cardiac surgery requiring bypass. Hydrocortisone also leads to improved UOP and more negative fluid balance at 48 hours. CPB and cardiac surgery induce AI as determined by ACTH stimulation testing, and hydrocortisone infusion may have a greater effect in the prevention of LCOS among this cohort. In this pilot study, prophylactic hydrocortisone was not associated with a reduction in mortality, duration of mechanical ventilation, or LOS. A larger study will be needed, both to confirm our positive findings and to determine whether these benefits translate to improvements in clinically important outcomes.

REFERENCES