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# Serum cortisol concentration with exploratory cut-off values do not predict the effects of hydrocortisone administration in children with low cardiac output after cardiac surgery

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## Abstract

**OBJECTIVES**: Low cardiac output syndrome is common after paediatric cardiac surgery. Previous studies suggested that hydrocortisone administration may improve haemodynamic stability in case of resistant low cardiac output syndrome in critically ill children. This study was set up to test the hypothesis that the effects of hydrocortisone on haemodynamics in children with low cardiac output syndrome depend on the presence of (relative) adrenal insufficiency.

**METHODS**: A retrospective study was done on paediatric patients who received hydrocortisone when diagnosed with resistant low cardiac output syndrome after paediatric cardiac surgery in the period from 1 November 2005 to 31 December 2008. We studied the difference in effects of treatment with hydrocortisone administration between patients with adrenal insufficiency defined as an exploratory cut-off value of total cortisol of <100 nmol/l and patients with a serum total cortisol of ≥100 nmol/l.

**RESULTS**: A total of 62 of patients were enrolled, meeting the inclusion criteria for low cardiac output syndrome. Thirty-two patients were assigned to Group 1 (<100 nmol/l) and 30 were assigned to Group 2 (≥100 nmol/l). Haemodynamics improved after hydrocortisone administration, with an increase in blood pressure, a decrease in administered vasopressors and inotropic drugs, an increase in urine production and a decrease in plasma lactate concentrations.

**CONCLUSIONS**: The effects of treatment with hydrocortisone in children with low cardiac output after cardiac surgery was similar in patients with a low baseline serum cortisol concentration and those with normal baseline cortisol levels. A cortisol value using an exploratory cut-off value of 100 nmol/l for adrenal insufficiency should not be used as a criterion to treat these patients with hydrocortisone.

**Keywords:** Low cardiac output syndrome • Paediatric cardiac surgery • Adrenal insufficiency • Hydrocortisone • Cortisol



## INTRODUCTION

Low cardiac output syndrome (LCOS) is common after paediatric cardiac surgery, with a prevalence of up to 25% [1–4]. The classic symptoms of LCOS are hypotension, tachycardia, oliguria and poor peripheral perfusion [3–5], which may result in organ dysfunction [4, 6]. In most patients with LCOS after cardiac surgery, the early use of inotropic treatment and volume administration are effective in stabilizing the haemodynamic state [1, 7, 8]. However, some patients with LCOS do not respond to fluid and inotropic treatment [1, 7–9]. A cause of this resistant LCOS could be (relative) adrenal insufficiency [8–11] with inadequate cortisol response considering the severity of illness and degree of stress [12, 13]. This clinical status is also known as critical illness-related corticosteroid insufficiency [14]. Previous studies suggest that hydrocortisone administration may improve haemodynamic stability in case of resistant LCOS in children and adults [1, 3, 5–10, 14, 15].

In this study, we retrospectively studied the effects of hydrocortisone treatment in paediatric patients with resistant LCOS after cardiac surgery. We hypothesized that hydrocortisone treatment would be more effective in improving haemodynamics in patients with relative adrenal insufficiency as reflected by low endogenous plasma cortisol concentrations. In our study, adrenal insufficiency was defined as a serum cortisol concentration with an exploratory cut-off value of <100 nmol/l.

## MATERIALS AND METHODS

### Patients

We retrospectively studied all consecutive patients admitted to the paediatric intensive care unit (PICU) of the Leiden University Medical Center, in Leiden, the Netherlands who received hydrocortisone for resistant LCOS after cardiac surgery in the period from 1 November 2005 to 31 December 2008. The Dutch legislation does not require informed consent for retrospective observational studies, provided results are treated anonymously. LCOS was defined as a syndrome with the following clinical symptoms: hypotension, tachycardia, oliguria, cold extremities with or without metabolic acidosis [1, 3, 4], an increase in lactate >2.2 mmol/l and/or base deficit of ≤2.5 mmol/l and inotropic requirements [any dose of (nor)epinephrine]. The decision to give hydrocortisone as a treatment in case of LCOS was at the discretion of the attending paediatric intensivist. Patients who had not undergone surgery, or who had a sepsis proven by blood cultures as a cause of LCOS were excluded. Also patients who did not meet the criteria of LCOS, or only received a single dose of hydrocortisone, or patients who were on hydrocortisone therapy before surgery, were excluded.

In our laboratory, the normal range for serum total cortisol is 100–600 nmol/l and adrenal insufficiency is considered present if baseline serum total cortisol is <100 nmol/l [11, 16]. While admitted in the PICU, the circadian rhythm is absent. The circulating levels of cortisol do not follow a circadian rhythm [17]. As a consequence, hydrocortisone suppletion is dosed four times a day in equal doses on our PICU as instructed by our consultant endocrinologists.

After enrolling patients meeting the inclusion criteria, we defined two groups based on the serum cortisol concentration with an exploratory cut-off value prior to hydrocortisone treatment.

Group 1 had a serum total plasma cortisol lower than 100 nmol/l. Group 2 had a serum total plasma cortisol higher than, or equal to 100 nmol/l.

### Data collection

The data were obtained by review of the patient's charts in the electronic Patient Data Management System (PDMS; MetaVision, *i*MD*soft*, MA, USA), including laboratory data, for 72 h after the first dose of hydrocortisone.

For both groups, general data were collected including age, gender, weight, cardiac anatomical diagnosis, type of surgical procedure, cardiopulmonary bypass (CPB), presence of genetic syndromes and/or non-cardiac anomalies, postoperative complications, length of PICU stay, survival, paediatric risk of mortality score III (PRISM III) and the paediatric risk of mortality 2 (PIM2). In our hospital, PRISM III and PIM2 are used to define retrospectively the quality of the PICU. All data were collected by review of medical charts of the intensivists, cardiologists, cardiothoracic surgeons and consultants. Mortality is defined as patients who died before hospital discharge or transfer to another hospital [18].

For both groups clinical information collected for 72 h after the first hydrocortisone dose included baseline serum total cortisol, systolic and mean blood pressure, heart rate, inotropic dosage, fluid resuscitation, urine production, peritoneal dialysis, lactate, base deficit, duration of intubation (in days), nitric oxide (NO) inhalation, white blood cell count, glucose and insulin treatment.

Heart rate and systolic and mean blood pressure were recorded every minute. Blood pressure data were obtained from a peripheral arterial catheter. Dopamine, dobutamine, milrinone and (nor)epinephrine were infused into a central venous catheter by calibrated infusion pumps. The dose administration of all medication was recorded in the PDMS at any time. The vasoactive drugs used in the first 72 h after the first hydrocortisone dose were quantified by using the vasoactive medication score of Wernovsky *et al.* [2, 15]: dopamine (X1) + dobutamine (X1) + milrinone (X15) + epinephrine (X100) + norepinephrine (X100) (all in μg/kg/min).

Urine output was recorded in PDMS every hour from continuous urine collection from a bladder catheter. Urine production was defined in ml/kg/h. Fluid administration was recorded in the PDMS and defined in ml/kg/h. The normal range for glucose in our laboratory is 3.5–5.5 mmol/l. Hyperglycaemia was treated with insulin in our PICU when the blood glucose concentration exceeded 10 mmol/l at two consecutive measurements. The normal range for white blood cell count is $4.0–10.0 \times 10^9$/l. As a selective pulmonary vasodilator, NO was given as a treatment for pulmonary hypertension [11].

### Statistical analysis

For all patients, information was gathered and directly abstracted into variables in Statistical Package for the Social Sciences (SPSS) 16.0 for Windows.

Data are given as mean ± SD or as median with range as appropriate. Differences in baseline characteristics were tested by the Mann–Whitney test. Analysis of the two groups with respect to the changes in clinical variables over time was done using mixed models analysis of variance. Differences between groups were considered statistically significant when $P < 0.05$.

## RESULTS

A total of 62 patients were enrolled meeting the inclusion criteria for resistant LCOS. Thirty-two patients were assigned to group 1 (<100 nmol/l) and 30 were assigned to group 2 (≥100 nmol/l). The median serum total cortisol in group 1 was 38.5 nmol/l (range 7–99 nmol/l). In group 2, the median serum total cortisol was 258.5 nmol/l (range 100–1032 nmol/l). The demographic and clinical characteristics for both groups are listed in Table 1. Median age in group 1 was 36 days (range 6–2318 days) and 322 days (range 4–1532 days) in group 2. Median bodyweight was 4.0 kg (range 2.3–21 kg) in group 1 and 7.9 kg (range 3.0–17.3 kg) in group 2. The neonatal period begins at birth and includes the first month of life. The proportion of neonates was comparable in both groups, seven patients in group 1, and five in group 2. All patients were diagnosed with a congenital heart defect and underwent cardiac surgery (Table 2). In group 1, five patients and three in group 2 had undergone cardiac surgery without CPB. All patients received dexamethasone preoperatively (0.5 mg/kg) as part of the anaesthesia protocol. No medication known to influence cortisol levels was used postoperatively in both groups. All

**Table 1:** Characteristics of patients presented as mean ± SD or median (range)

| | Group 1 ($n = 32$) | Group 2 ($n = 30$) | $P$-value |
|---|---|---|---|
| Age at surgery, median days | 36.5 (6–2318) | 322 (4–1532) | 0.08 |
| Weight, median kg | 4.0 (2.3–21) | 7.9 (3–17.3) | 0.04 |
| M/F | 20/12 | 17/13 | NS |
| ABP mean mean (mmHg) | 54 ± 8 | 56 ± 8 | 0.2 |
| Vasopressor medication index (μg/kg/min) | 25.4 ± 12.2 | 34.2 ± 24.4 | 0.2 |
| Nitric oxide (% patients) | 38 | 37 | 0.9 |
| Lactate (mmol/l) | 1.7 ± 1.4 | 2.2 ± 1.7 | 0.05 |
| Leucocytes ($\times 10^9$/l) | 12.5 ± 4.6 | 11.8 ± 4.5 | 0.3 |
| PRISM III | 8 (2–20) | 8 (1–22) | 0.8 |
| PIM2 | | | |
| ICU-LOS (days) | 13 (5–54) | 13 (5–40) | 0.8 |
| Time on ventilator (days) | 8 (2–38) | 9 (3–33) | 0.8 |
| Survival (%) | 100 | 100 | |

$P$-values by Mann–Whitney $U$-test or $\chi^2$.

**Table 2:** Cardiac surgery

| | Group 1 ($n = 32$) | Group 2 ($n = 30$) |
|---|---|---|
| PA-banding | | 1 |
| Modified Blalock–Taussig shunt | 5 | 2 |
| Glenn, Blalock–Taussig shunt, tricuspid valve repair | 1 | 1 |
| Norwood stage I, Sano shunt | 3 | 3 |
| Fontan, fenestration (mitral valve repair) | 6 | 4 |
| Repair tricuspid valve, removal valve of Eustachia | 1 | |
| Repair of TOF (±AVSD repair) | 1 | 2 |
| Mustard Rastelli | | 1 |
| Hemi Mustard Glenn Rastelli | | 2 |
| Truncus arteriosus repair | | 1 |
| Aortic arch reconstruction, PA banding, (atrioseptectomy/ASD repair) | 2 | |
| Aortic arch reconstruction, VSD/ASD repair, coarctectomy (repair tricuspid valve) | 1 | 1 |
| Aortic arch reconstruction, PAPVD repair, ASD repair | 1 | |
| Contegra/valve replacement, (±VSD repair) | | 4 |
| Arterial switch (±VSD repair) | | 2 |
| (extended) Ross | 1 | |
| Nikaidoh | 2 | |
| Ross-Konno, aortic arch reconstruction | 1 | |
| VSD repair, ASD repair, PDA closure | 2 | |
| AVSD repair | 2 | 3 |
| RVOT repair, VSD repair | | 1 |
| Other (all with CPB) | 3 | 2 |

PA: pulmonary atresia; VSD: ventricular septal defect; ASD: atrial septal defect; AVSD: atrioventricular septal defect; TOF: Tetralogy of Fallot; PAPVD: partial anomalous pulmonary venous drainage; RVOT: right ventricle outlet tract; PDA: persistent ductus arteriosus.

patients received inotropic drugs. All patients were intubated and mechanically ventilated.

Characteristics of both study groups are shown in Table 1. Median PRISM III score was similar in both groups, 8.0 (range 2–20) in group 1 and 8.0 (range 1–22) in group 2, $P = 0.8$. Median PIM2 in group 1 was −3.455 (range −1.493 to −5.025). Median PIM2 in group 2 was −3.172 (range −1311 to −4986), $P = 0.6$.

Lactate levels were higher in patients with a baseline cortisol >100 nmol/l (group 2) and there was a trend towards a higher need for vasopressors in these patients. Twelve patients in group 1 and 11 patients in group 2 were receiving inhaled nitric oxygen at the time of the initiation of hydrocortisone treatment.

The median dose of hydrocortisone in group 1 was $4 \times 45$ mg/m$^2$ (range 20–65) and $4 \times 48$ mg/m$^2$ (range 30–65) in group 2 ($P = 0.5$). Median time from surgery to first dose of hydrocortisone was 36 h in group 1 (range 16–156) and 36 h (range 16–108) in group 2 ($P = 0.4$). In both groups, administration of hydrocortisone was followed by a similar increase in arterial blood pressure and a decrease in the dose of administered vasopressors. The amount of blood products and colloids administered, urine output and plasma lactate levels after administration of hydrocortisone did not differ between both groups. In almost all patients, some elevation of plasma glucose concentrations was seen. In group 1, 10 patients (31.2%) and in group 2, 12 patients (40.0%) required insulin for a short period because of a repeated serum glucose of >10 mmol/l ($P = 0.480$). In both groups, one patient needed peritoneal dialysis, and was excluded from the urine output analysis because of anuria.

The median time to extubation was 8 (range 2–38) days in group 1and 9 (range 3–33) days in group 2, ($P = 0.8$). The ICU length of stay was not different between both groups [median and range 13 (5–54) and 13 (5–40) days for groups 1 and 2, respectively, $P = 0.8$]. All patients were alive at hospital discharge.

## DISCUSSION

In this study, we found that the circulatory response to hydrocortisone in paediatric patients with LCOS after cardiac surgery was not different in patients with low baseline plasma cortisol levels (<100 nmol/l) compared with patients with higher cortisol levels. To our knowledge, this is the first study on the influence of baseline cortisol on the haemodynamic effects of exogenous hydrocortisone in children with LCOS. Our results differ from earlier studies in adult patients with septic shock showing that the beneficial effects of corticosteroids were only seen in

patients with adrenal insufficiency [19], although this could not be confirmed in another large trial [19, 20].

This study does not permit any conclusions on whether corticosteroids are beneficial in such patients. We observed a decrease in the need for vasopressors and an increase in mean arterial blood pressure after hydrocortisone, but as no control patients were studied, we cannot exclude that this effect was independent of the administered corticosteroids. Corticosteroids are used commonly after cardiac surgery, with 97% of paediatric heart centres reporting the use of corticosteroids with CPB in one study [21] and more than half of children after cardiac surgery in 38 US hospitals being administered corticosteroids in another study [22]. Some uncontrolled studies suggested that hydrocortisone treatment was beneficial in neonates and infants with vasopressor-resistant hypotension [7, 8]. However, in a recent large multicenter study in children undergoing congenital heart surgery, no difference in mortality was found in a multivariate analysis accounting for potential confounders among corticosteroid recipients and non-recipients [22]. This makes it clear that the role of hydrocortisone in paediatric cardiosurgical patients is still a controversy and the indication is not strictly defined. Our results suggest that baseline cortisol levels should not be used to decide whether or not to treat such patients with corticosteroids.

When interpreting the results, some limitations of this study should be considered. First, due to its retrospective nature, no control group was present that was not treated with corticosteroids. Second, the study population could not be representative for other patients after cardiac surgery. Although the patients had undergone complicated surgical procedures, and all patients were dependent on fairly high doses of vasopressors, survival was 100% in both study groups. It cannot be excluded that baseline cortisol values may have a predictive value in patients after cardiac surgery with a poorer prognosis. Furthermore, we measured cortisol levels at random timepoints and used 100 nmol/l as a cut-off value for adrenal insufficiency. It is well known that a randomly taken total cortisol level has limited value to diagnose adrenal insufficiency [23]. Total cortisol includes both free and protein-bound cortisol, but only free cortisol is biologically active. Also, the cortisol response after stimulation with adrenocorticotropic hormone (ACTH) may be a better diagnostic tool to assess adrenal function. However, in clinical practice, LCOS represents a situation that should be treated rapidly, making ACTH stimulation tests impractical. Future studies are necessary to find out if other cut-off values may have a predictive value. The heterogeneity of the cardiothoracic surgeries could be a discussion point of this study. Finally, the median age at surgery in group 1 was lower than in group 2. It has been suggested that neonates are less capable of controlling inflammatory stress after surgery [24]. In the study of Nakamura *et al.* [24], plasma cortisol levels were significantly lower in neonates (all <6 days old) than in infants (>1 month) .

Boix-Oxhoa [25] showed that cortisol values and the stress response after surgery in neonates younger than 9–10 days are significantly different, but that there is no difference in adrenal response between neonates over 10 days, infants and adults. A cause of these low plasma cortisol levels could be an immature neuro-endocrine transmission system in neonates [25]. As the proportion of neonates was comparable in both groups (seven patients in group 1 and five patients in group 2), we believe that age was not an important confounder in this study.

## CONCLUSION

The effects of treatment with hydrocortisone in children with low cardiac output after cardiac surgery were similar in patients with low baseline cortisol levels compared with patients with normal or high baseline cortisol concentrations. Based on the findings of this study, we conclude that a serum cortisol concentration with an exploratory cut-off value of <100 nmol/l for adrenal insufficiency should not be used as criterion to treat patients with hydrocortisone supplementation.

**Conflict of interest:** none declared.

## REFERENCES

[1] Suominen PK, Dickerson HA, Moffett BS, Ranta SO, Mott AR, Price JF *et al*. Hemodynamic effects of rescue protocol hydrocortisone in neonates with low cardiac output syndrome after cardiac surgery. Pediatr Crit Care Med 2005;6:655–9.
[2] Wernovsky G, Wypij D, Jonas RA, Mayer JE Jr, Hanley FL, Hickey PR *et al*. Postoperative course and hemodynamic profile after the arterial switch operation in neonates and infants. A comparison of low-flow cardiopulmonary bypass and circulatory arrest. Circulation 1995;92: 2226–35.
[3] Hoffman TM, Wernovsky G, Atz AM, Kulik TJ, Nelson DP, Chang AC *et al*. Efficacy and safety of milrinone in preventing low cardiac output syndrome in infants and children after corrective surgery for congenital heart disease. Circulation 2003;107:996–1002.
[4] Jones B. Low cardiac output syndrome in children. Curr Anaesth Crit Care 2005;16:347–58.
[5] Hoffman TM, Wernovsky G, Atz AM, Bailey JM, Akbary A, Kocsis JF *et al*. Prophylactic intravenous use of milrinone after cardiac operation in pediatrics (PRIMACORP) study. Prophylactic intravenous use of milrinone after cardiac operation in pediatrics. Am Heart J 2002;143: 15–21.
[6] Pizarro CF, Troster EJ, Damiani D, Carcillo JA. Absolute and relative adrenal insufficiency in children with septic shock. Crit Care Med 2005; 33:855–9.
[7] Seri I, Tan R, Evans J. Cardiovascular effects of hydrocortisone in preterm infants with pressor-resistant hypotension. Pediatrics 2001;107: 1070–4.
[8] Noori S, Friedlich P, Wong P, Ebrahimi M, Siassi B, Seri I. Hemodynamic changes after low-dosage hydrocortisone administration in vasopressor-treated preterm and term neonates. Pediatrics 2006;118: 1456–66.
[9] Menon K, Lawson M. Identification of adrenal insufficiency in pediatric critical illness. Pediatr Crit Care Med 2007;8:276–8.
[10] Ando M, Park IS, Wada N, Takahashi Y. Steroid supplementation: a legitimate pharmacotherapy after neonatal open heart surgery. Ann Thorac Surg 2005;80:1672–8.
[11] Hatherill M, Tibby SM, Hilliard T, Turner C, Murdoch IA. Adrenal insufficiency in septic shock. Arch Dis Child 1999;80:51–5.
[12] Mesotten D, Vanhorebeek I, Van den Berghe G. The altered adrenal axis and treatment with glucocorticoids during critical illness. Nat Clin Pract Endocrinol Metab 2008;4:496–505.
[13] Cooper MS, Stewart PM. Corticosteroid insufficiency in acutely ill patients. N Engl J Med 2003;348:727–34.
[14] Marik PE, Pastores SM, Annane D, Meduri GU, Sprung CL, Arlt W *et al*. Recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients: consensus statements from an international task force by the American College of Critical Care Medicine. Crit Care Med 2008;36:1937–49.
[15] Shore S, Nelson DP, Pearl JM, Manning PB, Wong H, Shanley TP *et al*. Usefulness of corticosteroid therapy in decreasing epinephrine

requirements in critically ill infants with congenital heart disease. Am J Cardiol 2001;88:591–4.
[16] Arlt W, Allolio B. Adrenal insufficiency. Lancet 2003;361:1881–93.
[17] Paul T, Lemmer B. Disturbance of circadian rhythms in analgosedated intensive care unit patients with and without craniocerebral injury. Chronobiol Int 2007;24:45–61.
[18] Dorfman AT, Marino BS, Wernovsky G, Tabbutt S, Ravishankar C, Godinez RI *et al*. Critical heart disease in the neonate: presentation and outcome at a tertiary care center. Pediatr Crit Care Med 2008;9:193–202.
[19] Annane D, Sébille V, Charpentier C, Bollaert PE, François B, Korach JM *et al*. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. J Am Med Assoc 2002;288:862–71.
[20] Sprung CL, Annane D, Keh D, Moreno R, Singer M, Freivogel K *et al*. Hydrocortisone therapy for patients with septic shock. N Engl J Med 2008;358:111–24.
[21] Checchia PA, Bronicki RA, Costello JM, Nelson DP. Steroid use before pediatric cardiac operations using cardiopulmonary bypass: an international survey of 36 centers. Pediatr Crit Care Med 2005;6:441–4.
[22] Pasquali SK, Hall M, Li JS, Peterson ED, Jaggers J, Lodge AJ *et al*. Corticosteroids and outcome in children undergoing congenital heart surgery: analysis of the Pediatric Health Information Systems database. Circulation 2010;122:2123–30.
[23] Arafah BM. Hypothalamic pituitary adrenal function during critical illness: limitations of current assessment methods. J Clin Endocrinol Metab 2006;91:3725–45.
[24] Nakamura M, Suita S, Yamanouchi T, Masumoto K, Ogita K, Taguchi S *et al*. Cortisol and cytokine responses after surgery in different age groups of pediatric patients. Pediatr Surg Int 2003;19:194–99.
[25] Boix-Oxhoa J. Cortisol response to surgical stress in neonates. Pediatr Surg Int 1987;2:267–70.