Prognostic significance of serum cortisol in catecholamine-resistant pediatric shock

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Abstract

Objective: To determine prevalence of adrenal insufficiency in catecholamine-resistant pediatric shock; and to study association between serum cortisol level and severity of illness in catecholamine resistant pediatric shock.

Study design: Prospective observational study

Setting: Pediatric intensive care unit in a tertiary care hospital.

Patients: 114 pediatric patients with catecholamine refractory shock.

Interventions: Serum cortisol and outcome parameters of mortality, vasoactive inotropic score, Pediatric Risk of Mortality Score and mechanical ventilation rate were recorded.

Results: The prevalence of adrenal insufficiency in our study was 14.03%. Mortality as primary outcome variable was significantly correlated to age (0.737), weight (0.291), adrenal insufficiency (0.354), Pediatric Risk of Mortality Score (0.677), and vasoactive inotropic score (0.268). Increase in age, higher incidence of adrenal insufficiency and Pediatric Risk of Mortality Score were associated with the highest odds of dying with 13.7 (95% CI, 0.2-943), 2.36 (95% CI, 1.86-2.82) and 1.47 (95% CI, 1.16-1.86) respectively. Overall, the outcome variables were significant in patients with adrenal insufficiency and those with unusually high adrenal cortisol response.

Conclusion: We concluded, adrenal response is varied in a wide spectrum of disease conditions in critically ill children. Both low and abnormally high cortisol response to acute illness is associated with poor clinical outcome in the form of high mortality, increased need for catecholamines and higher rates of mechanical ventilation.

Keywords: Adrenal insufficiency, serum cortisol, catecholamine-resistant shock, vasoactive inotropic score, pediatric risk of mortality score

Introduction

Shock acts as a strong stimulator for the activation of the hypothalamic pituitary adrenal (HPA) axis, to increase serum levels of cortisol-releasing hormone, adrenocorticotropic hormone, and cortisol in acutely ill patients [1]. Patients that fail to optimally activate the HPA axis and consequent cortisol production during critical illness have higher mortality and morbidity [1, 2]. After initial enthusiasm regarding the role of steroids in shock waned because of various meta analysis showing no benefit [3], their use resurrected after 1990s, mainly in critical care situations [4]. The revived practice was based on the observations that a substantial increase in cortisol is expected in critical care situations, such as trauma, surgery, shock and others. Further, studies observed that some patients in critical situation exhibited a blunted cortisol response, which led some experts to propound a supplementation of cortisol in physiological doses to these patients [4]. The expression “relative adrenal insufficiency” was suggested to describe those critically ill patients who in absence of an underlying HPA axis insufficiency with septic shock; and to study association between serum cortisol level and severity of illness in catecholamine resistant pediatric shock.

Conclusion: We concluded, adrenal response is varied in a wide spectrum of disease conditions in critically ill children. Both low and abnormally high cortisol response to acute illness is associated with poor clinical outcome in the form of high mortality, increased need for catecholamines and higher rates of mechanical ventilation.

Keywords: Adrenal insufficiency, serum cortisol, catecholamine-resistant shock, vasoactive inotropic score, pediatric risk of mortality score

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There is also ambiguity in the 2008 and 2012 surviving sepsis guidelines for adults. While 2008 guidelines in adults suggest that AI on account of catecholamine-resistant septic shock is accepted at a random serum cortisol of < 18 mg/dL, 2012 sepsis guidelines suggest that inappropriately low random cortisol level (<18 mg/dL) in a patient with shock would be taken as an indication for initiating steroid therapy [19, 20]. Further, performing ACTH stimulation test is not recommended by these guidelines because two large studies on corticosteroids in sepsis did not show any interaction between hydrocortisone replacement and response to ACTH on mortality [21, 22].

The objectives of this study were to determine prevalence of AI in catecholamine-resistant pediatric shock; and to study association between serum cortisol level and severity of illness in catecholamine resistant pediatric septic shock, in the light of current guidelines.

Material and methods
This was a prospective longitudinal study conducted in the pediatric intensive care unit (PICU) of Department of Pediatrics at SKIMS, Srinagar, over a period of two years (January 2014- December 2015). One hundred and fourteen consecutive children in the age group of 1 month and 17 years, who had catecholamine refractory shock constituted the study group. We excluded patients who had received systemic steroids for more than 10 days in the previous month or had more than one dose of systemic steroids within the 24 hours before admission or patients with known central or primary AI. Shock was defined as per the American Academy of pediatrics practice guidelines. Shock was classified functionally into hypovolemic, cardiogenic, distributive and obstructive shock on the basis of history, clinical examination and bedside echocardiography. Catecholamine refractory shock was defined as persistent hypotension after adequate fluid resuscitation and titration of a single vasopressor. Our unit uses a protocolsed approach to septic shock according to the surviving sepsis guidelines [19]. Serum cortisol level was measured before starting the patients on hydrocortisone which was given as bolus of 100mg/mm² followed by 100mg/mm² per day divided every 4 hours. Hydrocortisone was discontinued if the random cortisol level drawn before the initial bolus was ≥18 μg/dl. Cortisol measurements were done using chemi-luminescent immunoassay method. Various authors in different studies have proposed varied definitions for AI [9, 10, 11]. We adopted 2012 sepsis guidelines to define AI as an inappropriately low random cortisol level (<18 mg/dL) in a patient presenting with shock [20].

Patient parameters recorded included: baseline characteristics (age, sex, weight, diagnosis), Pediatric Risk of Mortality Score (PRISM III), mechanical ventilation rates and vasoactive inotropic score (VIS). All parameters were recorded within the first 12 hours of PICU admission except PRISM-III score which was recorded within first 4 hours of admission [22]. The VIS was calculated by using the formula: dopamine (mg/kg/min) x1 + dobutamine (mg/kg/min) x1 + epinephrine(mg/kg/min)x100 + norepinephrine (mg/kg/min) x100 + phenylephrine (mg/kg/min) x100 + vasopressin(U/kg/min) x10,000 + milrinone (mg/kg/min)x10 [25-27]. The study was approved by hospital ethical committee.

The primary outcome measure was mortality. Secondary objectives were to determine the relationship of serum cortisol with clinically important parameters PRISM-III score, VIS and need for mechanical ventilation.

Statistical analysis:
Statistical Package for Social Sciences (SPSS) version 20 and XLSTAT 2016 were used for statistical analysis of the data. A logistic regression model using age, weight, AI, PRISM-III score and VIS as potential confounders was used to assess the relationship between different variables and mortality. Calibration of logistic model was assessed using the Hosmer-Lameshow goodness-of-fit test [28]. Results were presented as percent (%), median, interquartile range (IQR), and 95TH percent confidence interval (95th CI).

Results
During the study period 114 pediatric patients with catecholamine resistant shock met the eligibility criteria. Baseline patient characteristics are summarized in Table 1. Etiology of shock was septic in 90 (78.9%), cardiogenic in 20 (17.5%) and neurogenic in 4(3.5%) patients. Pneumonia (24%) was the most common underlying infection in septic shock. The etiology of cardiogenic shock was congenital heart lesions in 42.9% and dilated cardiomyopathy in 28.6% patients. The median (IQR) basal serum cortisol, PRISM-III score and VIS in our patients were 25 (21.6-32) μg/dl, 10(6-18) and 52.5 (10-185) respectively. Total of 51(44.7%) patients needed mechanical ventilation. The relationship of outcome variables with the type of shock is presented in Figure 1. On Spearman’s correlation mortality was found to be significantly correlated to age (0.737), weight (0.291), AI (0.354), PRISM-III (0.677), and VIS (0.268). All the variables found to be significantly correlated to the mortality, were entered into a logistic regression model. The Hosmer-Lameshow goodness-of-fit test showed that the model was well calibrated with a significant p-value of 0.112. All the variables remain independently associated with death. Increase in age, higher incidence of AI and PRISM-III were associated with the highest odds of dying with 13.7 (95% CI, 0.2-943), 2.36 (95% CI, 1.86-2.82) and 1.47 (95% CI, 1.16-1.86) respectively. The AI as defined by serum cortisol level of <18 mcg/dl (group-I) was observed in 16(14.03%) patients; serum cortisol of 18-45 mcg/dl (group-II) was observed in 80 (70.2%) patients; and cortisol of >45mcg/dl (group-III) was observed in 18(15.79%) patients. The overall mortality was 39.5%, being highest (45%) in cardiogenic shock followed by neurogenic shock (25%). Mortality was 75% in group-I, 27.5% in group-II and 61.1%. All the outcome variables of mortality. PRISM-III score, VIS and mechanical ventilation rate were significant in group-I and group-II. The median (IQR) cortisol in non-survivors and survivors was 21(6.6-50.09) mcg/dl and 31.99 (18.44-55.76) mcg/dl respectively (p=0.08).

Table 2 and Figure-2 depicts the comparison of PRISM-III and VIS between patients with AI and with no AI.
### Table 1: Baseline characteristics, therapy received and univariate comparisons between survivors and non-survivors

| Characteristic | All subjects (n=228) | Survivors (n=148) | Non-survivors* (n=80) | P value |
|----------------|----------------------|-------------------|------------------------|---------|
| **Age(months), median (IQR)** | 23.3(8-72) | 25.5(11.5-66) | 21.5(8-78) | 0.16 |
| **Male, no. (%)** | 121(53.1) | 77(52) | 44(55) | 0.82 |
| **Weight(kg), median (IQR)** | 11.2(5-18.6) | 11.8(7.6-16.5) | 11.2(6.5-17.2) | 0.85 |
| **Respiratory disease, no.(%)** | 148(64.9) | 103(69.6) | 45(56.2) | 0.37 |
| **Hemato-oncologic disease, no.(%)** | 31(13.6) | 17(11.5) | 14(17.5) | 0.32 |
| **Gastrointestinal disease, no.(%)** | 25(11) | 11(7.4) | 14(17.5) | 0.049 |
| **Renal disease, no.(%)** | 22(9.6) | 16(10.8) | 6(7.5) | 0.64 |
| **Vital signs, median (IQR)** | | | | |
| **Heart rate, beats/minute** | 167(134-214) | 164(126-188) | 173(138-206) | 0.55 |
| **Respiratory rate, breaths/minute** | 24(19-32) | 22(17-30) | 26(20-34) | 0.17 |
| **Systolic blood pressure, mmHg** | 102(89-116) | 102(87-114) | 102(90-116) | 0.82 |
| **Diastolic blood pressure, mmHg** | 66(50-80) | 66(50-78) | 66(50-80) | 0.87 |
| **Serum cortisol ( mcg/dl)** | | | | |
| **Baseline characteristics, therapy, and outcome comparisons between low(<18 mcg/dl) and normal(>18mcg/dl) baseline cortisol groups.** | | | | |
| **Laboratory values, median (IQR)** | | | | |
| **Hematocrit,%** | 29.1(20.2-57.1) | 32.1(24.1-53.2) | 37.1(25.2-47.3) | 0.37 |
| **Total leukocyte count, per mm³** | 4.6(2.1-20.6) | 5.6(1.8-19.6) | 3.2(2.3-13.5) | 0.042 |
| **Platelet count, per mm³** | 116(16-365) | 122(38-285) | 84(33-310) | 0.22 |
| **pH** | 7.21(6.9-7.34) | 7.24(7.1-7.28) | 7.10(7.0-7.18) | 0.014 |
| **Creatinine, mg/dl** | 1.10(0.41-3.72) | 0.9(0.42-2.4) | 1.14(0.67-3.8) | 0.061 |
| **Total bilirubin, mg/dl** | 1.10(0.41-3.72) | 0.84(0.44-4.46) | 1.30(0.64-4.82) | 0.065 |
| **Albumin, mg/dl** | 3.2(1.44-4.2) | 3.7(1.8-4.4) | 2.5(1.2-4.4) | 0.045 |
| **PRISM-III score, median (IQR)** | 12(8-18) | 10(8-15) | 18(9-22.5) | 0.004 |
| **PELOD score, median (IQR)** | 14(8.2-18) | 10.2(6.6-16.8) | 15.4(10-18.6) | 0.027 |
| **Serum cortisol ( mcg/dl)** | 25(20-30.2) | 25.6(21.6-28) | 20.5(4.3-35) | 0.080 |

**Therapy during first 72 hours**

| Additional fluids, ml/kg, median (IQR) | Cortisol <18 mcg/dl, n=46 | Cortisol>18mcg/dl, n=182 | P value |
|----------------------------------------|---------------------------|---------------------------|---------|
| 0-6 | 60(20-100) | 60(20-90) | 60(40-100) | 0.31 |
| 7-72 | 10(0-40) | 10(0-40) | 20(20-40) | 0.041 |
| **VITALS, median (IQR)** | | | | |
| **6 hours** | 95(10-240) | 40(10-210) | 110(65-220) | 0.007 |
| **24 hours** | 50(10-240) | 40(10-195) | 55.5(10-230) | 0.032 |
| **72 hours** | 30(10-150) | 20(10-100) | 30.5(0-150) | 0.037 |
| **Mechanical ventilation, no. (%)** | | | | |
| **0-6** | 90 | 47 | 43 | 0.041 |
| **7-72** | 39 | 18 | 21 | 0.032 |
| **Duration of hospital stay, days** | 17(9-28) | 22(10-30) | 16(6-72) | 0.082 |

**P value**

- mortality(non-survivors) corresponds to 60-day mortality
- IQR-interquartile range; CVP-central venous pressure; MAP-mean arterial pressure; PRISM-pediatric risk of mortality; PELOD-pediatric logistic organ dysfunction; VIS-vaso-active inotropic score.

### Table 2: Baseline characteristics, therapy, and outcome comparisons between low(<18 mcg/dl) and normal(>18mcg/dl) baseline cortisol groups.

| Characteristics | Cortisol <18 mcg/dl, n=46 | Cortisol>18mcg/dl, n=182 | P value |
|-----------------|---------------------------|---------------------------|---------|
| **Age(years), median (IQR)** | 24.2(8-80) | 23.2(11-76) | 0.21 |
| **Vital signs, median (IQR)** | | | |
| **GCS** | 7(4-13) | 9(5-13) | 0.91 |
| **Temperature, degree C** | 35.6(3-39.4) | 36.4(34.6-40.5) | 0.61 |
| **Heart rate, beats/minute** | 176(130-210) | 162(133-192) | 0.20 |
| **CVP, mmHg** | 4.4(3.2-5.5) | 3.6(3.1-6.4) | 0.84 |
| **MAP, mmHg** | 48.3(33.5-64.5) | 54.2(36.2-66.5) | 0.61 |
| **PRISM-III, median (IQR)** | 11(8-18.5) | 15(9-22) | 0.12 |
| **Laboratory values, median (IQR)** | | | | |
| **Hematocrit,%** | 33.8(24.2-48.6) | 32.2(26.2-52.2) | 0.61 |
| **Total leukocyte count, per mm³** | 2.8(1.3-13.5) | 5.4(2.8-19.2) | 0.058 |
| **Platelet count, per mm³** | 68(32-260) | 122(36-292) | 0.11 |
| **pH** | 7.06(6.9-7.2) | 7.20(7.0-7.28) | 0.014 |
| **Creatinine, mg/dl** | 1.11(0.63-3.9) | 0.9(0.46-3.4) | 0.088 |
| **Total bilirubin, mg/dl** | 1.20(0.60-3.74) | 0.86(0.44-3.6) | 0.071 |
| **Albumin, mg/dl** | 2.5(1.4-3.8) | 3.2(2.0-4.5) | 0.076 |
| **Prothrombin time, seconds** | 26(16-58.5) | 17(13-45) | 0.011 |
| **Lactate on admission,mmol/L, median (IQR)** | 4.7(4.2-6.6) | 4.2(3.5-5.9) | 0.14 |
| **Therapy during first 72 hours** | | | |
| **Additional fluids, ml/kg, median (IQR)** | 60(40-100) | 60(20-90) | 0.48 |
| **0-6** | 66(20-320) | 60(102.2-280) | 0.22 |
| **7-72** | 57.5(12-230) | 40(210) | 0.27 |
### Table

| VIS, median (IQR) | 6 hours | 24 hours | 72 hours | Mechanical ventilation, no.(%) |
|-------------------|---------|----------|----------|---------------------------------|
| 0-6               | 26.5(0-150) | 98       | 74       | 46                              |
| 7-72              | 8       | 24       |          | 49                              |

### Outcome

| PELOD score, hours, median (IQR) | Duration of hospital stay, days | Mortality, no(%) | In-hospital | 60-day |
|----------------------------------|---------------------------------|------------------|-------------|--------|
| 0 (10-18.8)                      | 24                              | 19               | 5           |        |
| 6 (10.1-17.4)                    | 56                              | 43               | 13          |        |
| 24 (9.5-16.6)                    | 14.5 (10.1-18.8)                | 12               | 5           |        |
| 48 (8.2-16.5)                    | 11.5 (8.2-16.5)                 | 8.4              | 4           |        |
| 72 (4.3-18.5)                    | 10.5 (7.1-16.2)                 | 8.5              | 3           |        |

### Figures

**Fig 1:** Outcome Parameters in different types of shock

**Fig 2:** Comparison of Pediatric Risk of Mortality Score (PRISM-III) and vasoactive inotropic score (VAS) in patients with and without adrenal insufficiency. PRISM-III- Pediatric Risk of Mortality Score; VIS- vasoactive inotropic score; AI-adrenal insufficiency;
 Discussion
We observed an overall mortality of 39.5% in patients with shock. Septic shock was the predominant (78.9%) clinical type and pneumonia (24%) was the most common underlying infection. Fisher et al. in their study on clinical spectrum of shock in pediatric patients reported septic shock as the underlying physiology in 57% of cases, followed by hypovolemic and distributive shock [29]. Pneumonia as the most common underlying infection in septic shock was consistent with the findings in other studies [30]. In our study the mortality was highest (45%) in cardiogenic shock followed by neurogenic shock. In critically ill pediatric patients, cardiogenic shock represents 5-13% of diagnosed cases of shock [29]. It is the most advanced and most serious stage of heart failure. When associated with extracardiac comorbidities (sepsis, acute renal failure, liver failure), the mortality rate can increase by fivefold [31]. Although cardiogenic shock is fatal in 5–10% of cases who need hospitalization, the high mortality in our patients can be explained by the fact that our patient population contained high number of unoperated and complicated congenital heart diseases [31]. Further, the majority of the shock patients were in decompensated stage at admission and often complicated by extracardiac comorbidities. Further, we recruited a relatively sick patient cohort for study as supported by high PRISM-III score, VAS, and higher rates of ventilation; which perhaps accounted for overall higher mortality in our study as against existing literature [32].

The optimum range for serum cortisol in patients with shock remains unclear [19, 20]. In addition, the lack of uniform criteria for diagnosis of AI in shock has lead to the reported incidence varying from 4.5 to 41.9% on admission [19, 20, 33]. The prevalence of AI in our study was 14.03%, consistent with existing literature. We observed a mortality of 75% in patients with AI, statistically higher than those with adequate adrenal response. Sarthi M and colleagues studied adrenal status in children with septic shock using low dose ACTH (1mcg) stimulation test and observed a mortality of 56% in patients with AI [12]. They further reported that 6 (75%) of the 8 children with catecholamine refractory shock died compared with 9(41%) of 22 with catecholamine responsive shock (p = 0.09). They used basal cortisol levels <7 mcg/dL and/or peak cortisol level <18 mcg/dL as the criteria for AI [12].

Eighteen (15.8%) study patients had unusually high serum cortisol (>45mcg/dl [34]) response on admission. Out of these 11 (61%) patients died during the hospital stay. The observed high mortality in patients with cortisol of >46mcg/dl was consistent with the findings of Susan S Sam et al., who reported 81% mortality in patients with cortisol level >1242nmol/l (45mcg/dl) [35]. D’Ananne and colleagues observed that values of serum cortisol >34mcg/dl or even 45mcg/dl were significantly associated with high death rates and concluded that the basal serum cortisol rises with the severity of illness and correlates with high mortality in various critically ill patients [36]. The association of high cortisol with high mortality as reported in our study, is perhaps related more to the severity of underlying illness, rather than due to the direct deleterious effect of high serum cortisol, as supported by other studies [34].

We reported a significantly high median (IQR) PRISM-III score in patients with adrenal insufficiency and those with unusually high serum cortisol response. Recently, there have been multiple changes to the data collection process for the PRISM score [24]. First, the time period for measuring PRISM has changed [24]. Physiologic variables are measured only during the first four hours of intensive unit care, to best separate the predictor variables from any bias due to therapy [24]. Second, only the first intensive unit admission in any hospitalization is included and outcome is predicted at hospital discharge, rather than ICU discharge [37]. We recorded the physiological variables at the time of admission to PICU and the outcome was measured for the total stay in the hospital, which included ICU and non-ICU care. Mark Hatherill and coworkers in a study on AI in septic shock reported similar observations of significantly high PRISM in patients with AI [18(9-36) vs 12(4-26)] [38]. As their observation was based upon the first 24 hours of PICU physiological data, they concluded that pre-admission stabilization might result in artificially low PRISM scores [38].

We used the vasoactive-inotropic Score (VIS) as an objective clinical tool to quantify the need of cardiovascular support in patients with shock. VIS has been used as a predictor of morbidity and mortality in children in septic shock and after cardiac surgery [26, 39]. We reported a significantly higher median (IQR) VIS in group-I and group-III. Most of the studies have used the number of catecholamines as the tool to assess the need for cardiovascular support in patients with AI [12, 33]. Pizarro CF et al. in a study on 57 patients with septic shock observed that all children with fluid-responsive shock had adequate cortisol response (>9 microg/dL) and those with AI had a higher risk of catecholamine resistant shock (RR, 1.88; 95% CI, 1.26-2.79) [11].

The rate of mechanical ventilation in our study patients in group-I and group-III were 81.2% and 72.2% respectively, significantly higher than those with optimal adrenal response. Chung-Jen Huang and Horng Chuyan Lin in a prospective, randomized study observed that the successful ventilator weaning percentage was significantly higher in patients with adequate adrenal reserve (88.4%) than those with AI (68.6%) [40]. They concluded that for patients with respiratory failure, early identification of AI and appropriate supplementation with stress dose hydrocortisone increase the success of ventilator weaning and shortens the weaning period [40].

Our study had many limitations. Study sample size was smaller. Single measurement of cortisol was taken from catecholamine resistant shock patients, no repeat assays were done to monitor the response to management. ACTH stimulation test was not done, and response to IV steroids was not documented.

We concluded, adrenal response is varied in a wide spectrum of disease conditions in critically ill children. Both low and abnormally high cortisol response to acute illness is associated with poor clinical outcome in the form of high mortality, increased need for catecholamines and higher rates of mechanical ventilation. Despite the correlation between serum cortisol and clinically important outcome parameters, it is difficult to usefully estimate the appropriate cortisol response that children with critical illness should mount during shock. There is need for further research to demonstrate such adequate cortisol response and larger studies are needed to demonstrate the cut-off values in pediatric shock patients above or below which mortality increases significantly.
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