Egyptian Pediatric Association Gazette (2014) **62**, 18–23

Contents lists available at ScienceDirect

Egyptian Pediatric Association Gazette

journal homepage: http://ees.elsevier.com/epag

Adrenocortical status in infants and children with sepsis and septic shock☆

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Received 8 January 2014; revised 3 February 2014; accepted 5 February 2014
Available online 26 February 2014

KEYWORDS

Adreno-cortical state;
Corticosteroids;
Pediatric ICU;
Relative adrenal insufficiency;
Septic shock

Abstract *Background:* The benefit from corticosteroids remains controversial in sepsis and septic shock and the presence of adrenal insufficiency (AI) has been proposed to justify steroid use.
Aim: To determine adrenal state and its relation with outcome in critical children admitted with sepsis to PICU of Cairo University, Children Hospital.
Methods: Thirty cases with sepsis and septic shock were studied. Cortisol levels (CL) were estimated at baseline and after high-dose short ACTH stimulation in those patients and in 30 matched controls. Absolute AI was defined as basal CL < 7 μg/dl and peak CL < 18 μg/dl. Relative AI was diagnosed if cortisol increment after stimulation is < 9 μg/dl.
Results: Overall mortality of cases was 50%. The mean CL at baseline in cases was higher than that of controls (51.39 μg/dl vs. 12.83 μg/dl, $p = 0.000$). The mean CL 60 min after ACTH stimulation was higher than that of controls (73.38 μg/dl vs. 32.80 μg/dl, $p = 0.000$). The median of %rise in cases was lower than that of controls (45.3% vs. 151.7%). There was a positive correlation between basal and post-stimulation cortisol with number of system failure, inotropic support duration, mechanical ventilation days, and CO_2 level in blood. There was a negative correlation between basal and post stimulation cortisol with blood pH and HCO_3.
Conclusion: RAI is common with severe sepsis/septic shock. It is associated with more inotropic support and has higher mortality. Studies are warranted to determine whether corticosteroid therapy has a survival benefit in children with RAI and catecholamine resistant septic shock.

Introduction

Despite the advances in intensive care, septic shock and severe sepsis remain a major cause of morbidity and mortality. In fact, the incidence of septic shock and severe sepsis has been increasing over the past 30–40 years. It is estimated that in the USA there are about 750,000 new cases of severe sepsis every year.[1]

Patients with septic shock manifest an overwhelming inflammatory response to the infection; the body then regulates this response by producing anti-inflammatory cytokines which is manifested by a period of immune-depression.[2]

☆ The work was performed at PICU of New Children's Hospital, Cairo University's hospitals, Cairo, Egypt.

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Peer review under responsibility of Egyptian Pediatric Association Gazette.

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http://dx.doi.org/10.1016/j.epag.2014.02.001

Despite that the most common cause of adrenal insufficiency is sepsis and systemic inflammatory response syndrome (SIRS), there is a great controversy about using corticosteroids as one of the treatment options in children with sepsis and septic shock.[3] Some studies found that the use of corticosteroids produced no change in mortality rates or could even increase as a result of secondary infection.[4] On the other hand, many studies have reported better evolution when corticosteroids were used.[5]

Corticosteroids act by correcting a state of adrenal insufficiency, inhibiting synthesis of inducible nitric oxide synthase (iNOS) leading to reduced production of nitric oxide and hence lesser vasodilatation, restoring the sensitivity of vascular catecholamine receptors and decreasing the transcription of inflammatory cytokines. Steroids have been shown to improve blood pressure, reduce the prevalence of post-traumatic stress disorder and improve the emotional well-being of survivors of septic shock. Despite these potential advantages, still steroids are indicated in only those patients with septic shock who have failed to respond to vasopressors.[6]

Methodology

Objectives

We aimed in this work to assess the presence of clinical or subclinical adrenal insufficiency (evidenced by reduced cortisol and/or reduced responsiveness to Adreno-Corticotropin Hormone) in children with SIRS and septic shock.

Patients

This prospective clinical study was conducted in a tertiary pediatric intensive care unit, in Cairo University, children hospital.

The study included 30 patients with severe sepsis and 30 healthy controls of matching age for comparison.

Inclusion criteria

- Patients Aged between 2 months and 15 years suspected to have SIRS; meeting SIRS criteria are considered as having at least 2 of the following 4 clinical parameters abnormal[7]:
  (a) Body temperature (temperature >100.4 °F (38 °C) or temperature <96.8 °F (36 °C).
  (b) Heart rate (HR > 90/min).
  (c) Respiratory rate [RR > 20/min or PaCO2 < 32 mmHg (4.3 kPa)].
  (d) Peripheral leukocytic count (WBC $< 4\times10^9$/L (<4000/mm^3), $>12\times10^9$/L ($>12{,}000$/mm^3), or 10% bands).

The International Pediatric Sepsis Consensus has proposed some changes to adapt these criteria to the pediatric population.[8]

In children, the SIRS criteria are modified in the following fashion:

- Heart rate is greater than 2 standard deviations above normal for age in the absence of stimuli such as pain and drug administration, or unexplained persistent elevation for greater than 30 min to 4 h. In infants, also includes Heart rate less than 10th percentile of age in the absence of vagal stimuli, beta-blockers, or congenital heart disease or unexplained persistent depression for greater than 30 min.
- Body temperature obtained orally, rectally, from Foley catheter probe, or from central venous catheter probe less than 36 °C or greater than 38.5 °C. Temperature must be abnormal to qualify as SIRS in pediatric patients.
- Respiratory rate greater than 2 standard deviations above normal for age or the requirement for mechanical ventilation not related to neuromuscular disease or the administration of anesthesia.
- White blood cell count elevated or depressed for age not related to chemotherapy, or greater than 10% bands plus other immature forms.[8]
- Or sepsis as defined by the presence of infection in association with criteria meeting SIRS.
- Or severe sepsis which is defined as evidence of end-organ dysfunction such as altered mental status, episode of hypotension, elevated creatinine or evidence of disseminated intravascular coagulopathy.
- Or septic shock as defined by persistent hypotension despite adequate fluid resuscitation or tissue hypo perfusion.[9]

Exclusion criteria

- Patients with Pre-existing condition associated with dysfunction of hypothalamo–pituitary–adrenal axis.
- Any use of corticosteroids during the 2 weeks preceding this episode.
- Patients with known primary immune deficiency disorders.

Patients were subjected to

(a) Clinical assessment including full history and thorough physical examination.
(b) Routine Laboratory tests (arterial blood gases, complete blood picture including differential count, C-reactive protein, liver function tests, renal function tests and coagulation profile).
(c) Assessment of the severity of the condition including:
- Presence or absence of mechanical ventilation.
- Level of inotropic support.
- Severity of illness in the 1st 24 h after diagnosis of septic shock as assessed by pediatric risk of mortality (PRISM) type3.
- Length of stay in pediatric intensive care unit

(d) Cultures from blood and from suspected site of infection.
(e) Radiography (chest X-ray) and others as needed according to infection site.

Specimen collection and intervention

(a) Blood samples were obtained within 24 h of admission for measurement of basal cortisol and adreno-corticotropin hormone by radio-immuno-assay, results were compared with those of normal controls.

(b) The ACTH stimulation test can be given as a *low-dose short test*, a *conventional-dose short test*, or as a *prolonged-stimulation test*. In the low-dose short test, 1 μg/kg of an ACTH drug is injected into the patient. In the conventional-dose short test, 250 μg of drug is injected. Both of these short tests last for about an hour and provide the same information. The prolonged-stimulation test, which is also called a *long conventional-dose test*, can last up to 48 h.[10] A study has shown that the low dose ACTH stimulation test is more sensitive and specific,[11] while other studies showed that the cortisol response of the adrenals is the same for the low-dose and conventional-dose tests.[12,13] We used the standard (conventional) synthetic adreno-corticotropin hormone stimulation test was performed with intravenous administration of 250 μg of synthetic adreno-corticotropin hormone followed by serum cortisol level measurement 60 min afterward.
(c) Pre and post samples were 2 cc venous samples each.
(d) The samples were centrifuged immediately and the sera of the samples were preserved at temp less than 20 °C.
(e) Serum Cortisol levels were estimated using the IMMULITE technique at endocrinology lab of the hospital.
(f) The specimens were diluted, and the assays were repeated if the cortisol values were > 50 μg/dl.
(g) Basal cortisol levels < 7 μg/dl and/or post stimulation cortisol level < 18 μg/dl were used to define absolute adrenal insufficiency.[14] We considered diagnosis of relative adrenal insufficiency if the increment in cortisol was < 9 μg/dl after stimulation.[15]
(h) No changes in the standard treatment protocol used in this PICU were made based on the results of the adrenal function tests. This protocol described giving hydrocortisone to patients diagnosed to have SIRS or septic shock.
(i) The protocol was approved by department of pediatrics at Children Hospital of Cairo University and informed parental consent was taken.

Follow up to determine progression and the need for respiratory and circulatory support and to determine survival to discharge and duration of hospitalization

Controls

We have got control samples from children coming to outpatient clinic, short history and clinical examination were taken to confirm that they did not suffer from SIRS or infection

Statistical analysis

Data were tabulated and analyzed using appropriate methods. Quantitative data were expressed as mean and standard deviation (SD), and means were compared using T test. Correlation between numerical values and comparison of non-numerical values using Chi square test were done. P values < 0.05 considered significant.

Results

The study included 30 controls and 30 cases. Their ages ranged from 3 months to 5 years; with a median of 7.5 (4–17) months. The majority of cases were suffering from pneumonia (63.3%) followed by gastroenteritis (20%). While regarding the main causes of ICU admission, 76.7% were in respiratory distress or failure, and 63% had circulatory failure (septic shock). The characteristics of the cases studied are summarized in Table 1.

Table 2 shows basal and post-stimulation serum cortisol levels in cases and controls.

Regarding controls, the median of percent rise was 151.7% (108.2–207.4) highly significant ($P = 0.0000$). While for cases, the median post-stimulation rise was 45% (16.5–69.2); this difference was also statistically significant ($p = 0.006$).

We found that the median of basal and post-stimulation cortisol levels in cases (47.3 μg/dl and 62 μg/dl; respectively) was higher than those of the controls (13 μg/dl and 31.9 μg/dl; respectively), $p = 0.00$.

No cases or controls had absolute adrenal insufficiency. Ten cases (33.3%) were suffering from relative adrenal insufficiency defined as a post-stimulation rise less than 9 μg/dl. No controls had relative adrenal insufficiency ($p = 0.0003$).

There was a significant positive correlation between basal and post-stimulation cortisol levels ($r = 0.82$, $p < 0.0001$) as shown in Fig. 1. There was a negative correlation ($r = -0.46$, $p = 0.01$) between basal cortisol and percent rise post-stimulation.

The results of the mean basal cortisol levels were higher in patients who died than those who survived, $p = 0.03$. The

Table 1 Characteristics of cases studied.

	Number	Frequency
Gender		
Male	18	60
Female	12	40
Need for Mechanical Ventilation	17	57
Need for Cardiovascular support		
Volume expansion (> 20 mL/Kg)	15	50
Dopamine	21	70
Dobutamine	19	63.3
Noradrenaline	4	13.3
Adrenaline	3	10
Culture-proven infection	15	50
Gram −ve infections	8	26.6
Gram +ve infections	3	10
More than one organism	4	13.4

Table 2 Basal and post-stimulation serum cortisol levels in cases and controls.

Cortisol (μg/dl)	Mean	SD	95%Cl	Min	Max
Controls					
Basal	12.83	1.86	12.16–13.49	9	16
Post-stimulation	32.80	6.43	30.50–35.1	21	49.6
Percent rise	161.75	67.95	137.4–186.1	61.9	323.9
Cases					
Basal	51.39	30.01	40.65–62.12	17	150
Post-stimulation	73.38	29.75	62.74–84.02	35.10	150
Percent rise	63.61	80.71	34.73–92.49	0	342.86

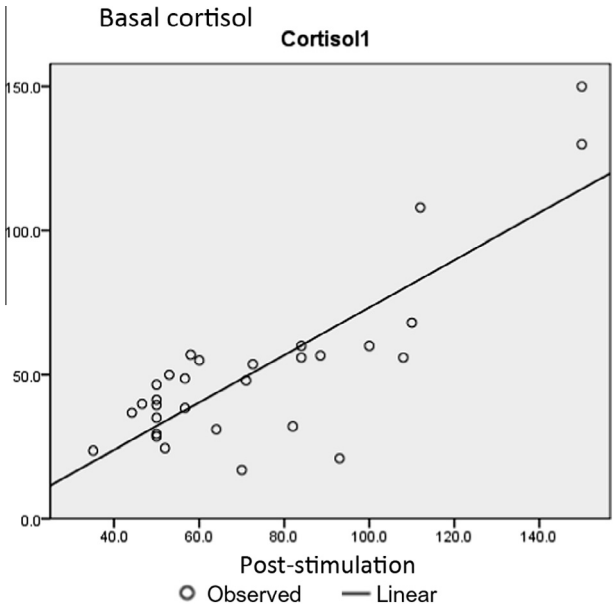


Figure 1 Correlation between basal and post-stimulation cortisol levels ($r = 0.82$, $p < 0.0001$).

values of the mean post-stimulation cortisol were also higher in those who died but the difference was not reaching significance, $p = 0.06$. (Fig. 2)

The total mortality in our cases was 50%. In the patients suffering from relative adrenal insufficiency, 70% died (7 cases), and 30% survived ($p = 0.06$). (Fig. 3)

The duration of inotropic support and the number of system failure had a significant positive correlation with both basal and post-stimulation cortisol levels ($p = 0.04$ and 0.02; respectively) and ($p = 0.02$ for both). On the other hand, no significant correlation was found with mechanical ventilation, length of ICU stay and total antibiotic days.

Higher basal cortisol can predict mortality as shown in Fig. 4. The higher basal cortisol was insignificantly associated with relative adrenal insufficiency; i.e. those with higher basal tended to have more adrenal insufficiency. (Fig. 5)

Discussion

The prevalence of pneumonia followed by gastroenteritis was in accordance with being the commonest sites of infection in infants and children.[16] Moreover, gram −ve bacteria were more prevalent than gram +ve ones. Similarly, Kang and colleagues (2011) found that septic shock was a common finding in patients with gram −ve bacteremia.[17] This can be explained by the fact that gram −ve bacteria contain Lipo-polysaccharide which is associated with the release of excessive cytokines in the circulation leading to vigorous systemic inflammatory response.[18]

In the present study, the mean basal and post-stimulation cortisol levels were significantly higher in patients suffering from sepsis and septic shock when compared with controls. Same results were concluded in a study done by Elfaramawy (2012).[19]

Sarthi and colleagues (2007) reported higher mean basal cortisol levels (71 μg/dl vs. 51 μg/dl) and post stimulation cortisol levels (91 μg/dl vs. 51 μg/dl) than those of our study.[15] Whereas Zhang and colleagues (2008) reported mean basal (35.6 μg/dl) and post stimulation (51.7 μg/dl) cortisol level lower than that of our study.[20] The difference in the degree of hypercorticism both at the basal and stimulated states might be attributed to the difference in the severity of infections in patients enrolled in different studies.

In Sarthi et al. (2007) study, all patients had septic shock (100%)[15], meanwhile, the proportion of cases with septic shock in our study was 43.3% while only 14.5% of the patients studied by Zhang and colleagues (2008) had septic shock.[20]

We reported positive correlations between basal and post-stimulation cortisol levels and the severity of the condition which is reflected by the number of system failure and duration of inotrope requirement.

Morbidity and mortality were associated with basal and post stimulation cortisol levels in cases.

The positive relation between basal and post-stimulation cortisol levels in relation to cases' outcome was attributed to the more stressful condition in patients who died in comparison to those who improved and discharged. The mean of the percent rise in those who died was less than that of survived ones.

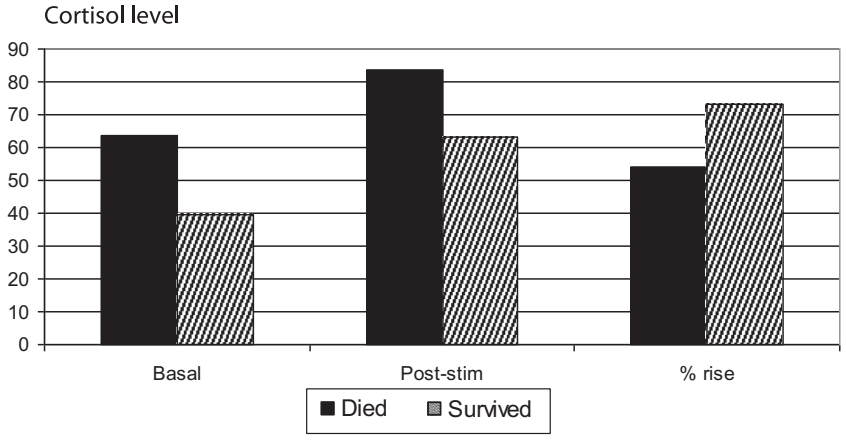
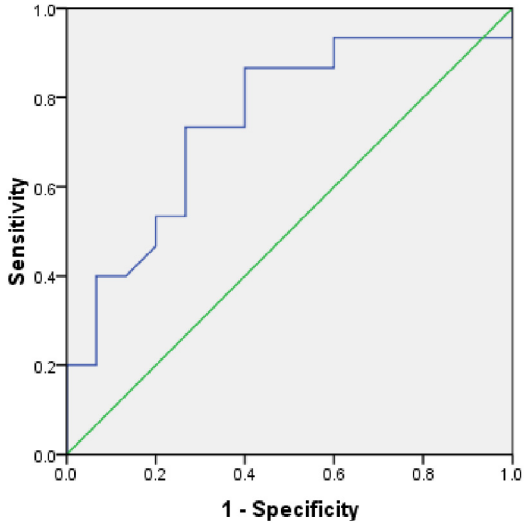


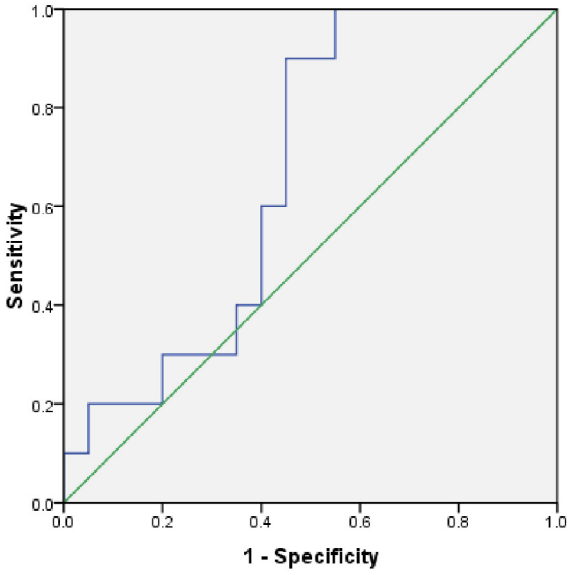
Figure 2 Comparison of cortisol levels between cases who survived and those who died.

Figure 3 Relative adrenal insufficiency and outcome of the patients.



AUC =0.749; p=0.02
Cut-off 47.3 (sens=73.3%, Sp=73.3%)

Figure 4 ROC curve: basal cortisol as a predictor of death.



AUC =0.67; p=0.135
Cut-off 39.7 (sens=90%, Sp=55%)

Figure 5 ROC curve: basal cortisol as a predictor of relative adrenal insufficiency.

The positive correlation found between basal and post stimulation cortisol levels and the number of system failure in the patient, can be explained by the high stress added by the presence of system failure. This stress leads to elevation of basal and post-stimulation cortisol levels, and lower percent rise due to high basal cortisol level that cannot increase any more after stimulation. In agreement with our study, all patients who died at Casartelli et al. study (2007) showed baseline cortisol level higher than 25 μg/dl and Kolditz et al. (2010) showed that serum cortisol levels were significantly elevated in both patients with critical pneumonia and those who died.[21,22]

Although Hebbar and colleagues (2012), found that 75% of their cases met the definition for AAI, none of our patients met the diagnostic criteria of AAI.[23]

The RAI in our study (33.3%) was in agreement with Sarthi et al. (2007) (30%) and Zhang et al. (2008) (40.3%).[15,20] On the other hand, Elfaramawy (2012) reported RAI in 66.6% of cases and Casartelli et al. (2007) in 77.3%.[19,21]

All patients diagnosed to have SIRS or septic shock received hydrocortisone according to the protocol approved in this PICU. No treatment was added after doing the ACTH stimulation test.

In our study 70% of those with RAI died. This was similar to Sarthi et al. (2007) who found that 56% of cases with RAI died.[15]

Conclusions and recommendations

Most of our cases were suffering from one or more system failure especially circulatory failure; this contributes to the high mortality rate. Those with RAI had higher basal and post-stimulation cortisol levels in comparison to the controls.

As the percent rise of controls was higher than that of cases, we conclude that sepsis is associated with decreased percent rise of cortisol level.

Higher mortality rates were found with inotropic support and mechanical ventilation.

We recommend further studies to correlate the effect of giving steroids in treatment of relative adrenal insufficiency aiming to decrease the duration of inotropic support, mechanical ventilation and mortality.

We do not recommend the routine use of corticosteroids in critically ill patients with various grades of sepsis, as the basal and post-stimulation cortisol levels were high.

Authors' contribution

HR: data analysis, and participated in its design and coordination and helped to draft the manuscript. Y.A.: revision of the written paper. H.B.: recruitment of patients. M.H.: participated in the design of the study and performed the statistical analysis. All authors read and approved the final manuscript.

Conflict of interest

The authors declare that they have no competing interests.

Acknowledgement

We like to acknowledge all the patients who participated in the study, their parents and the nursing staff in the PICU.

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