EVALUATION OF THE HYPOTHALAMIC-PITUITARY-ADRENAL AXIS IN A PAEDIATRIC INTENSIVE CARE UNIT

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Abstract

Background. Relative adrenal insufficiency (RAI) is the inadequate production of cortisol due to dysfunction of the hypothalamic–pituitary–adrenal (HPA) axis during a severe illness. We evaluated the HPA axis and RAI in a tertiary pediatric intensive care unit (PICU).

Methods. A total of 100 PICU patients were included in this prospective cohort study. Basal serum levels of adrenocorticotrophic hormone (ACTH), cortisol values were compared with those in the control group. A low-dose ACTH stimulation test was performed in patients with basal cortisol levels below 18 µg/dL.

Results. The basal cortisol levels of the PICU patients were significantly higher than those of the control group ($P < 0.05$). All tested patients ($n = 24$) had delta cortisol levels > 9 µg/dL and a peak cortisol response > 18 µg/dL. Basal cortisol levels were positively correlated with Pediatric Risk of Mortality (PRISM) III scores ($P < 0.05$; $r = 0.363$). The basal or stimulated cortisol levels of the patients who received glucocorticoid treatment were higher than the cut-off levels.

Conclusions. High basal or stimulated cortisol levels are indicative of disease severity in the acute phase of stress. Patients with very high cortisol levels should be particularly carefully monitored because of the high mortality risk.

Key words: adrenal insufficiency, cortisol, critical illness, pediatric risk of mortality score.

INTRODUCTION

Adrenal insufficiency is a critical condition that can lead to death when untreated in intensive care patients. Fluid- and catecholamine-resistant hypotension and hemodynamic instability are the most common findings in intensive care patients with adrenal insufficiency (1). Critical illnesses such as major surgery, sepsis, septic shock, infectious diseases, and trauma are the most common causes of severe physical

stress leading to impaired hemodynamic homeostasis. During acute stress, glucocorticoid, mineralocorticoid, and catecholamine synthesis increase due to the activation of the hypothalamic–pituitary–adrenal (HPA) axis, thus providing stress adaptation and physiological organ responses (2). The most effective glucocorticoid is cortisol. Cortisol has positive effects on vascular tone, the distribution of fluids within the vascular compartment, vasoconstrictor action of catecholamines, gluconeogenesis, glycogenolysis, and modulation of the immune response (3). During severe illness, there is inadequate production of cortisol due to dysfunction of the HPA axis and peripheral resistance to glucocorticoids. This condition is called critical illness-related corticosteroid insufficiency or relative adrenal insufficiency (RAI) (4). Clinically apparent adrenal insufficiency is usually rare in critically ill patients (5). Adrenal function is usually assessed by measuring the serum concentrations of total cortisol, free cortisol, or salivary cortisol levels (6). Random cortisol measurement and adrenocorticotrophic hormone (ACTH) stimulation tests have been used to diagnose RAI. There are many criteria for diagnosing RAI, including basal serum levels of cortisol ≤ 10 µg/dL, or poor cortisol response to ACTH stimulation tests (delta cortisol increment < 9 µg/dL or peak cortisol ≤ 18 µg/dL) (7). Low - (1 µg) or high-dose (250 µg) ACTH tests can be used; however, the low-dose test may be more physiologically relevant (8,9). Most practitioners make recommendations for glucocorticoid replacement treatment according to the clinical condition of patients, and not based on ACTH stimulation tests in intensive care units. In this cross-sectional prospective study, we investigated the HPA axis based on basal and stimulated serum levels of cortisol in patients with different diagnoses in our pediatric intensive care unit (PICU).

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MATERIALS AND METHODS

Subjects

This prospective study was performed in the PICU of Eskisehir Osmangazi University Hospital. We included all patients between 1 and 18 years of age admitted to the PICU during the study period. The exclusion criteria were known HPA disease and the use of one dose systemic steroids (except for dexamethasone) during the previous 24 hours or more than 10 days in the previous month before referral to the hospital, which affects basal and post-ACTH stimulation test results. The control group consisted of healthy children who were similar to the patient group in terms of age and sex who applied to the outpatient clinic with the aim of monitoring height and weight. Informed consent was obtained from the parents of patients and healthy children.

Definition of variables

Severity of illness was defined by the Pediatric Risk of Mortality III (PRISM III) score between 8 and 24 h following PICU admission by a pediatric intensive care specialist. PRISM III is a validated predictor of prognosis and expected risk for mortality based on clinical and laboratory findings, such as blood pressure, heart rate, respiratory rate, pupillary reactions, partial CO₂, Glasgow coma score, serum levels of total bilirubin, potassium, and blood coagulation tests (10). Higher PRISM III scores indicate greater severity of illness. Sepsis was defined according to the Third International Consensus Definitions for Sepsis and Septic Shock criteria (11). An axillary temperature $\geq 38.5^{\circ}\text{C}$ was indicative of fever, serum levels of C-reactive protein (CRP) > 0.5 mg/dL indicated CRP positivity, serum levels of eosinophils $> 5\%$ indicated eosinophilia, and blood gas pH < 7.30 or HCO₃ < 15 indicated acidosis. Blood samples were obtained from patients between 8:00 and 9:00 a.m. in the first 24 h after admission. Basal serum levels of cortisol, ACTH, glucose, and electrolyte levels were measured. A low-dose (1 μg) ACTH stimulation test was performed in patients

with basal cortisol levels < 18 $\mu\text{g/dL}$. Peak cortisol was the level after 30 min of intravenous ACTH administration, and delta cortisol was the difference between the basal and peak levels. RAI was defined as peak cortisol levels < 18 $\mu\text{g/dL}$ or delta cortisol levels < 9 $\mu\text{g/dL}$ following ACTH stimulation. ACTH measurements were performed using a cobas e 411 analyzer (Roche Diagnostics, Basel, Switzerland), and cortisol values were measured using an electrochemiluminescence immunoassay on a Cobas e 602 analyzer (Roche). Clinical and laboratory outcome data were obtained from medical records.

Statistical analysis

Statistical tests were performed using the SPSS 21.0 package (IBM Corp, Armonk, NY, USA). Descriptive statistics were gathered. Data are expressed as the mean $\pm$ standard deviation (SD). Comparisons between groups were conducted using the Mann–Whitney U test and Student's t-test. The relationships between PRISM III scores and basal cortisol levels, and ACTH and basal cortisol levels were examined using linear regression analyses. A P-value < 0.05 was considered significant.

RESULTS

Patient characteristics

A total of 100 patients (45 females) and 35 healthy children (similar ages and sex) were enrolled in the study. The control group consisted of healthy subjects without any known acute or chronic disease applying to the outpatient clinic for growth monitoring. Patient characteristics are shown in Table 1, and the primary diagnoses of the patients are given in Table 2. Of the 100 patients, 23% had infectious diseases, 17% had neurological diseases, 13% had cardiac diseases, 15% were intoxicated, 14% had sepsis, and 18% were admitted for other diseases (such as gastrointestinal bleeding, renal insufficiency, diabetic ketoacidosis, and autoimmune hemolytic anemia). Most of the infectious diseases were of the respiratory tract. None of the cardiac disease patients had

Table 1. Clinical and laboratory parameters of patients

	Mean $\pm$ SD	Minimum - Maximum
Age (year)	7.0 $\pm$ 6.16	0.3–17
Weight (kg)	28.4 $\pm$ 23.48	3.1–85
Duration of intensive care unit (day)	4.4 $\pm$ 4.92	1–3
PRISM III mortality score	7.07 $\pm$ 7.31	0–42
ACTH (pg/mL)	16.9 $\pm$ 18.1	1–111
Basal cortisol ($\mu\text{g/dL}$)	28.06 $\pm$ 19.23	4.6–145.0
Eosinophil (%)	1.19 $\pm$ 1.99	0.0–10.9

Table 2. Basal cortisol, ACTH test and PRISM III scores according to primary disease

Primary diagnosis	(n)	Basal cortisol ($\mu\text{g/dL}$)	PRISM III score
		Mean $\pm$ SD	Mean $\pm$ SD
Neurological disease	17	27.14 $\pm$ 7.18	7 $\pm$ 5.51
Cardiac disease	13	35.56 $\pm$ 35.39	15.84 $\pm$ 11.73
Intoxication	15	19.01 $\pm$ 10.59	3.66 $\pm$ 4.16
Sepsis	14	37.12 $\pm$ 28.41	8.42 $\pm$ 4.58
Infectious disease	23	29.70 $\pm$ 12.70	6.26 $\pm$ 5.74
Other	18	21.91 $\pm$ 8.64	3.61 $\pm$ 5.32
Total	100	28.06 $\pm$ 19.23	7.07 $\pm$ 7.31

Figure 1. Comparison means basal cortisol levels of disease groups.

recently undergone operations before hospitalization. Thirteen of the intoxicated patients were suffering from drug intoxication, and two were suffering from carbon monoxide intoxication. Nine patients were on mechanic ventilation. None of the patients had a history of receiving systemic steroids in the last three months before admission. Eleven of 100 patients (11%) received glucocorticoids in their first week in the ICU; 3 of these patients (renal insufficiency secondary to nephrotic syndrome, autoimmune hemolytic anemia and acute lymphoblastic leukemia) were on maintenance therapy, and the others received glucocorticoid therapy for the treatment of shock. Electrolyte levels were normal in all patients except for one with renal insufficiency. Four patients had eosinophilia. Corticosteroids lead to eosinopenic effects by stimulating eosinophil apoptosis. The presence of eosinophilia in critically ill patients is associated with clinical signs of adrenal insufficiency (5). All albumin levels were >2.5 mg/dL.

Cortisol levels

The basal cortisol levels were significantly higher in patients than in controls ($P < 0.05$) (Table 3).

According to primary diagnosis, the sepsis and cardiac disease groups had higher cortisol levels than the other groups, whereas the intoxication group had the lowest levels (Fig. 1). A positive correlation was observed between basal cortisol levels and PRISM III mortality scores ($P < 0.05$; $r = 0.36$) (Fig. 2). There was a very weak positive correlation between basal cortisol and ACTH levels ($P > 0.05$; $r = 0.17$) (Fig. 3). The cortisol levels were higher in CRP-positive patients than in CRP-negative patients ($P < 0.05$). In patients who needed inotropic treatment support, they were higher than in patients who did not need inotropic support ($P < 0.05$) (Table 3). Serum cortisol levels were significantly higher in patients who did not undergo low-dose ACTH stimulation test ($P < 0.05$) (Table 3). There was no difference between basal cortisol levels of patients with and without eosinophilia (Table 3). Six patients died during the study period in the PICU. In these six patients, cortisol levels were at the median level of 36.9 $\mu\text{g/dL}$ (35.8 – 41.3). None of the deceased patients underwent lowdose ACTH stimulation testing. No correlations were found between patient age, weight, sex, duration of stay in the PICU, and cortisol levels. There were no significant differences between respiratory support, fever, acidosis, and cortisol levels.

Low-dose ACTH stimulation test

In 24 of the 100 patients, basal cortisol levels were <18 $\mu\text{g/dL}$, and thus they underwent a low-dose ACTH test. All tested patients had delta cortisol levels > 9 $\mu\text{g/dL}$ and a peak cortisol response > 18 $\mu\text{g/dL}$. The mean stimulated cortisol level of patients who underwent a low-dose ACTH stimulation test was 40.39 ± 25.48 $\mu\text{g/dL}$ (min: 20–max: 143) (Table 4). The mean stimulated cortisol level was 47.95 ± 15.4 $\mu\text{g/dL}$ in the neurological disease group (n:2), 49.4 ± 24.3 $\mu\text{g/dL}$ in the cardiac disease group (n:3), 29.72 ± 10.27 $\mu\text{g/dL}$ in the intoxication group (n:7), 45.55 ± 9.12 $\mu\text{g/dL}$ in the sepsis group (n:2), 36.2 ± 6.7 $\mu\text{g/dL}$ in the infectious diseases group (n:4), and 46.88 ± 25.48 $\mu\text{g/dL}$ in the other disease group (n:6).

Table 3. Comparisons and outcomes

	n	Basal cortisol Mean $\mu\text{g/dL}$ ($\pm$ SD)	P value
Patient	100	28.06 ± 19.23	
Control	35	15.05 ± 4.09	0.007*
ACTH test			
yes	24	10.3 ± 3.5	
no	76	33.68 ± 18.75	0.000*
Fever			
yes	20	31.88 ± 28.31	
no	80	27.73 ± 16.72	0.919*
CRP			
positive	43	29.37 ± 12.1	
negative	54	26.72 ± 23.7	0.009*
Acidosis			
yes	21	29.37 ± 11.8	
no	69	27.89 ± 21.4	0.788*
MV			
yes	9	41.73 ± 33	
no	91	26.7 ± 16.9	$>0.05^\dagger$
IS			
yes	21	42 ± 33.4	
no	78	24.35 ± 10.8	0.02*
Eosinophilia			
yes	4	32.03 ± 19.22	
no	96	29.43 ± 20.11	$>0.05^\dagger$
Survive			
Yes	94	27.61 ± 19.6	
no	6	35.13 ± 8.18	$>0.05^\dagger$

CRP, C-reactive protein; MV, mechanic ventilation; IS, inotropic support

Data are presented as mean $\pm$ SD, while comparison was performed using*Independent sample t-test or † Mann Whitney U test according to the distribution of the data.Table 4.** Low-dose ACTH stimulation test results

	mean $\pm$ SD (min-max)
0. min cortisol ($\mu\text{g/dL}$)	10.3 ± 3.5 (5.2-17.1)
30. min cortisol ($\mu\text{g/dL}$)	40.39 ± 25.48 (20-143)
Delta cortisol	29.6 ± 12.5 (11.1-133.5)

DISCUSSION

CRH and ACTH secretion are increased by HPA activation in the early phase of acute and severe stress. Peripheral resistance, abnormal glucocorticoid activity in the tissue, and inhibition of negative feedback to cortisol also contribute to high cortisol levels (12). However, serum levels of cortisol may be normal, high, or low in adrenal insufficiency (13,14). High levels reflect severe stress and low levels indicate a reduced stress response. In our study, the basal levels were measured in the first 24 h of hospitalization, and were higher in patients than in healthy controls. Cortisol production is the most important defensive mechanism against stress, particularly after acute hemodynamic changes in

Figure 2. Correlation between basal cortisol and PRISM III score ($r=0.36$) in the linear regression analysis. **Figure 3.** Correlation between basal cortisol and ACTH ($r=0.17$) in the linear regression analysis.

the cardiovascular system. The basal level also reflects the intensity of stress. Our findings and those of other studies (1, 15-17) confirm that basal cortisol levels are significantly higher in patients under severe stress than in controls. Our findings may be partially attributable to the fact that we sampled blood in the early phase of stress. Michalaki *et al.* demonstrated that cortisol levels were significantly higher in the acute phase of stress (first day) than in the recovery phase (days 5 and 6) (15). Menon *et al.* demonstrated that basal levels were higher in patients diagnosed with adrenal insufficiency than in patients without adrenal insufficiency during the first 24 h of admission to the PICU (1). Balboa *et al.* found that children with critical illnesses had significantly higher baseline levels than those in controls on the first

day of admission; our results are consistent with this (16).

In a previous study, RAI frequency was reported to be 17–75% based on basal cortisol threshold levels (7). When RAI is defined as delta cortisol levels $< 9 \mu\text{g/dL}$ following an ACTH stimulation test, this rate ranges from 12.5% to 50% (17–19). There is no consensus for RAI diagnosis in children. The most commonly used approach is to perform an ACTH stimulation test if a random cortisol level is between 10 and $34 \mu\text{g/dL}$. In this study, we accepted a cut-off of $18 \mu\text{g/dL}$ for basal cortisol. In 24 of the 100 patients (24%), a basal level $< 18 \mu\text{g/dL}$ was detected. However, in all patients, delta cortisol was $> 9 \mu\text{g/dL}$ or the peak cortisol response was $> 18 \mu\text{g/dL}$ following low-dose ACTH stimulation tests. The RAI ratio in our study was lower than those found in other studies. We believe that cortisol values may have been reduced due to decreased production and suppression of the HPA axis after a longer critical illness period. Thus, we may detect higher RAI ratios if we study the late phase of stress. In addition, some patients underwent a low-dose ACTH stimulation test, and this created limitations in determining the frequency of RAI.

Primary diagnosis and disease severity affect cortisol levels in intensive care patients. Very low or high cortisol levels are associated with increased mortality risk. The mortality risk is higher if basal cortisol levels are above $34 \mu\text{g/dL}$ (20). During the study period, six patients died during follow-up. Four of the deceased patients had serious congenital heart disease and the others were diagnosed with sepsis and multiple congenital anomalies. The basal cortisol levels in these six patients were higher than $34 \mu\text{g/dL}$. There was also a positive correlation between basal cortisol and PRISM III scores in all of the patients. Based on these observations, basal cortisol and PRISM scores may be used as predictive markers in the PICU. Aydın *et al.* detected a positive correlation between PRISM III scores and basal cortisol levels in 40 patients who were followed from their first day of admission in the PICU (21). Iyer *et al.* reported a positive correlation between peak cortisol levels and PRISM III scores in children with fluid- and catecholamine-refractory shock; our study is in accordance with these findings (22).

In our study, patients diagnosed with sepsis or cardiovascular disease had higher serum levels of basal cortisol, whereas patients hospitalized due to intoxication had lower levels than the other groups. This may be because patients diagnosed with sepsis or cardiovascular disease have higher PRISM III scores and consequently higher disease severity. On the other hand, the PRISM score was lower in patients

hospitalized due to intoxication, and they faced only a mild or moderate severity of stress.

Some studies have investigated the predictive factors of RAI. Cortisol provides cardiovascular stabilization during stress. The need for inotropic support and high doses of inotropic drugs is an indicator of adrenal insufficiency in ICU patients (23–25). Oboni *et al.* examined the predictive factors of adrenal insufficiency in patients presenting with urgent complaints and found that eosinophilia was associated with adrenal insufficiency, whereas acidosis and CRP elevation were not (26). In our study, patients who needed inotropic drug treatment and who were CRP-positive had higher basal cortisol levels. These findings suggest that these patients may have faced more severe stress than patients who did not need inotropic treatment or who had negative CRP tests. In this study, patients diagnosed with cardiovascular disease or septic syndrome required inotropic support treatment. All of the patients with eosinophilia, high fever, metabolic or respiratory acidosis, or who required mechanical ventilation support had reasonable basal cortisol levels. Thus, none of these parameters can be used as indicators of RAI.

Glucocorticoid treatment tends to be administered according to the clinical conditions of patients in the ICU, and not based on the ACTH stimulation test or basal cortisol levels (22). As observed in our study, the basal and stimulated cortisol levels of all patients were reasonable.

In conclusion, high basal or stimulated cortisol levels indicate disease severity in the acute phase of stress. Patients with very high cortisol levels should be particularly carefully monitored because of their risk for mortality. The decision to administer glucocorticoid treatment should be planned according to the PRISM III score calculated on the basis of the patient's condition at admission to the intensive care unit. Cortisol levels are positively correlated with PRISM III mortality scores. HPA axis activity is complex during stress due to critical illnesses, and is affected by many factors. Further investigations are required to clarify the pathophysiology of the HPA axis during critical illness.

Conflict of interest

The authors declare that they have no conflict of interest.

Financial disclosure

No financial or non-financial benefits have been received or will be received from any party related directly or indirectly to the subject of this article. Permission was obtained from the ethics committee of Osmangazi University Medical Faculty with number 80558721/77 for this study.

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