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ORIGINAL ARTICLE

Serum Cortisol Level in Combination with High Adrenocortico-trophic Hormone Concentrations are Associated with Poor Outcome in Critically Ill Children

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ABSTRCT

Background: Cortisol is one of the major hormones in stress condition to maintain the hemostasis in the body. The severity of disease is associated with cortisol level in the blood, there is dissociation between adrenocorticotropic hormone (ACTH) and cortisol level in blood. This study aimed to evaluate serum cortisol level and adrenocorticotropic (ACTH) level in critically ill children.

Methods: The present study was case control that was conducted in pediatric intensive care unit (PICU), pediatric department, Zagazig University children hospital in period between July 2017 to January 2018. 64 infants and children admitted to (PICU) in the study. They were randomly divided into 2 groups. Group 1 included (24 males & 20 females) Group 2 included 20 healthy control subjects matched in age and sex. All patients are subject to: blood pressure control, heart rate, respiratory rate and temperature measurement. Lab investigation included CBC, albumin, CRP and blood culture, basal cortisol and ACTH.

Results: Mean ACTH at patients group was 21.7 ± 6.47 pg/ml and 11.3 ± 8.64 pg/ml in control group. Mean basal cortisol was 25.8 ± 4.62 ug/dl and 9.26 ± 1.95 ug/dl in group (1) and (2), respectively. The mean serum albumin in groups (1) and (2) was 3.16 ± 0.96 g / dl and 4.10 ± 0.45 g / dl. There was a statistically significant difference between the group of patients and the serum cortisol and ACTH controls ($p<0.001$). Among group (1) there were 34 patients survived represented 77.3% and 10 patients died represented 22.7%.The mean ACTH of survived patients was 20.9 pg/ml and mean cortisol was 24.8 ug/dl, while mean ACTH and mean cortisol among non-survived patients was 29.7 pg/ml and 40.9 ug/dl respectively .

Conclusion: In critically ill adolescents, high levels of serum cortisol in combination with high concentrations of adrenocorticotrophic hormone are associated with poor results.

Keywords: Critically ill pediatric patients, CRP, ACTH, cortisol.

INTRODUCTION

Critical ill infants and children have a significant response to stress that stimulates the axis of hypothalamic-pituitary-adrenal (HPA) [1]. In order to describe inadequate response to stress, the words "relative adrenal insufficiency" and critical illness related corticosteroid insufficiency" (CIRCI) are added. [2]. Nevertheless, the adequacy of glucocorticoid response to stressful situations in critically ill patients has not been identified yet. Multiple parameters were used to describe adrenal insufficiency in this population, including low basal serum total cortisol [< 275 nm (10µg / dl) or < 500 nm (18 µg / dl)] and high cortisol response to exogenous adrenocorticotropic hormone (ACTH)

stimulation [increase of approximately 250 nm (9 µg/dl) or < 500 nm (18 µg/dl)]. One of the controversial issues in both adult and pediatric critical care drugs is the concept of adrenal dysfunction. [3]. Total plasma cortisol in critically ill infants and children with hemodynamic instability is often assessed in order to select those most likely to benefit from systemic steroid treatment [4]. The meanings of normal and abnormal total plasma cortisol levels in this population remain controversial; a low level of cortisol could be interpreted as an indicator of inadequate stress response (relative adrenal insufficiency) or as a sign of lower physiological stress and thus a stable environment. Similarly, a high level of cortisol can indicate an adequate or impaired response to physiological stress [5]. In the absence of proven diagnostic criteria for CIRCI in children, the prevalence rates reported in various studies vary considerably, i.e. between 17% and 90% [6]. As a result, no agreement was reached on the reason for corticosteroid therapy, and studies on the correlation of adrenal activity with clinical outcome remained contradictory[7]. The objective of this research was to evaluate adrenal function in children hospitalized in pediatric intensive care unit (PICU) with an acute critical disease by assessing their total plasma cortisol and ACTH levels and to establish the relation between their total plasma cortisol levels and their clinical outcomes.

MTHODS

The present study was case control study conducted on group (1) contained 44 critically ill children admitted to pediatric intensive care unit (PICU) in period between July 2017 to January 2018 and group (2) contained 20 healthy patients as control group who were examined for their basal cortisol and ACTH to determine cortisol and ACTH variation in critical illness and healthy patients and its outcome.

Ethical Clearance: Written Informed consent was taken from the patient parents to participate in the study. Approval for performing the study was obtained from Pediatrics and Clinical Pathology Departments, Zagazig University Hospitals after taking Institutional Review Board (IRB) approval. The work has been carried out in accordance with the code of ethics of the world medical association (Decleration of Helsinki) for studies involving humans. The age of 44 critical ill infants and children ranged from one month to 12 years, they were 24 males and 20 females represented the group (1) and 20 healthy control subjects represented group (2) matched in age and sex .

Inclusion criteria: All critical ill children admitted to PICU at the time of study , their age ranged from 1 month to twelve years old .

Exclusion criteria: Patients with trauma-related secondary adrenal insufficiency or hypothalamic, adrenal or liver disease. Any use of corticosteroid during the 2 weeks preceding this episode. Patients used drugs that cause adrenal insufficiency such as Imidazoles, Etomidate, phenytoin, phenobarbital or carbamazepine, in the preceding three months. Immunosuppression of any last month's infection with etiology, human immunodeficiency virus, chemotherapy, or radiotherapy. Suspected or confirmed patients with asthma.

Methods: All patients included in the study were subjected to the following:

Full medical history taking, including past history of previous admission to PICU, previous cortisol therapy during two weeks preceding admission. Assessment of vital signs included blood pressure, heart rate, respiratory rate and temperature. Laboratory finding: CBC, albumin and CRP. Determination of basal blood cortisol and ACTH.

Assessment of adrenal function:

Serum Cortisol and ACTH levels were estimated using electro-chemiluminescene Immunoassay Cobas e602 Immunoassay Analyzer (Roche diagnostic Gmbh). The specimens were diluted, and the assays were repeated if the cortisol values were >50 ug/dl. Cortisol levels were measured by a chemiluminescent method (Immulite 2000; Diagnostic Products Corporation, Los Angeles, Calif).

STATISTICAL ANALYSIS

All data were collected, tabulated and statistically analyzed using SPSS version 22. Continuous quantitative variables e.g. ages were expressed as the mean ± SD & range, and categorical qualitative variables were expressed as absolute frequencies and relative percentage. Continuous data were checked for normality by using kolmogorv-Smirnov test. Independent samples Student's t-test was used to compare the two groups of normally distributed data. Categorical data were compared using Chi-square test (χ^2 test). All tests were two-sided p-value <0.05 was considered statistically significant (S), and p value of ≥ 0.05 was statistically non-significant (NS).

RESULTS

The study included 44 patients (group 1), they were 24 (54.5%) males with mean age±SD of 48.8 ± 14.7 months and 20 (45.5%) females with a mean age±SD of 46.7±12.9 months. Patients were compared with 20 apparently healthy infants and children used as control group (2); they were 10 males and 10 females with mean age ± SD of 37.9

± 11.8 and 39.2 ± 11.6 months, respectively (table 1). The weight of the patients was ranged from 8.2 – 30.6 Kg with mean ± SD of 10.5 ± 2.3 Kg while the control group had weight of 8.5 – 32.9 Kg with mean ± SD of 11 ± 3.5 Kg **(table 1)**.

In this study, the laboratory data showed that the mean CRP level was 65.8 ±3.48 mg/L and 58.9 ± 2.44 mg/L in group (1) and (2), respectively. They showed a statistically significant difference (P >0.05). The mean TLC was 15.6 ± 3.94 x10^9/L and 18.5 ± 4.12 x10^9/L in groups (1) and (2), respectively. They showed a statistical significance between the two groups (P = 0.04). The mean serum albumin was 3.16 ± 0.96 g/dl and 4.10 ± 0.45 g/dl in groups (1) and (2), respectively. They showed a statistically significant difference (P = 0.001). Both the critically ill children and the control groups showed a statistically non-significant difference (P >0.05) as regard temperature, systolic, diastolic blood pressure and respiratory rate **(table 2)**, but there were significant difference between two group regarding heart rate.

Mean serum ACTH at the patients' group was 21.7 ± 6.47 pg/ml and the control group showed a mean of 11.3 ± 2.14 pg/ml. The mean basal cortisol was 25.8 ± 4.62 ug/dl and 9.26 ± 1.95 ug/dl in group (1) and (2). All hormonal parameters in **table (3)** showed a statistically significant difference between the patients' group and the control group (p<0.001). As regarding outcome, 10 children out of 44 (22.7%) of the critically ill children died, by comparing serum cortisol level, it was found that it was significantly higher among non-survivors compared to that of survivors (40.9±7.4 versus 24.8 ± 4.5 respectively). Also, ACTH was significantly higher among non-survivors compared to survivors (29.7 ± 5.3 versus 20.9 ± 3.4 respectively). **table (4)** A cutoff point of cortisol value of 35 µg/dL or greater is predictor for increased mortality. **table (5)**

This study found serum cortisol operating characteristics (ROC) after the adrenocorticotropic hormone (ACTH) test to predict the need for vasoactive or inotropic help (area below curve 0.75). A 600nmol/L or higher baseline cortisol level is a predictor of increased mortality. **(Figure.1)**

Table (1): Demographic data of the studied group

Variable	Patients' group (1) mean ± SD (n = 44)		Control group (2) mean ± SD (n = 20)	
Age: (months)	48.8 ± 14.7		37.9 ± 11.8	
● **Males**	46.7 ± 12.9		39.2 ± 11.6	
● **Females**				
Weight: (Kg)	3.62 - 55.9		4.11 - 57.9	
● **Range**	21.2 ± 12.3		25.6 ± 14.5	
Duration of PICU stay (days):	10 – 40			
● **Range**	20.3 ± 3.67			
Sex:	**No.**	**%**	**No.**	**%**
● **Male**	24	54.5	10	50.0
● **Female**	20	45.5	10	50.0

Table (2): Laboratory and clinical data of the studied group

Variables	Group (1) (mean ± SD) (n = 44)	Group (2) (mean ± SD) (n = 20)	t-test	P value
CRP (mg/L)	65.8 ± 3.48	58.9 ± 2.44	0.6541	0.064
TLC (10^9/L)	15.6 ± 3.94	18.5 ± 4.12	2.254	**0.044***
WBC (10^6/L)	12.34 ± 2.52	12.93 ± 2.61	0.6667	0.066
Platelets (10^3/L)	167.6 ± 51.5	240.3 ± 36.6	7.323	**0.0023***
S. Albumin (g/dL)	3.25 ± 0.64	1.12 ± 0.25	3.0945	**0.032***
S. Lactate (mg/dL)	17.9 ± 1.35	18.2 ± 1.28	2.9562	0.091
Temperature (°C)	38.3 ± 1.02	37.2 ± 0.67	0.0684	0.654
Heart rate (BPM)	110.5 ± 21.03	95.6 ± 19.7	0.0622	0.571
Respiratory rate	38.1 ± 9.88	36.7 ± 8.89	0.0752	0.620
SBP (mmHg)	88.9 ± 12.2	85.5 ± 10.9	0.0655	0.612
DBP (mmHg)	52.3 ± 9.54	51.8 ± 8.97	0.0323	0.725

SBP: systolic blood pressure DBP: diastolic blood pressure

Table (3): Hormonal levels of the studied groups

Variable	Group (1)	Group (2)	t-test	P value
ACTH (pg/ml)	21.7 ± 6.47	11.3 ± 8.64	8.557	**0.0007***
Basal serum cortisol (µg/dL)	25.8 ± 4.62	9.26 ± 1.95	9.128	**0.0000***
Serum albumin (g/dl)	3.16 ± 0.96	4.10 ± 0.45	6.262	**0.0012***

* Statistically significant difference

Table (4): Outcome of the critically ill children

Variable	Group (1)	Group (2)	test	P value
Survivors	34 (77.3%)	20 (100%)	5.387	**0.02***
Non-survivors	10 (22.7%)	0 (0%)		

* Statistically significant difference

Table (5): hormonal levels of survivors and non-survivors among critically-ill children

Variable	Survivors (n=34)	Non-survivors (n=10)	test	P value
ACTH (pg/ml)	20.9 ± 3.4	29.7 ± 5.3	-6.815	**0.000***
Basal serum cortisol (µg/dL)	24.8 ± 4.5	40.9 ± 7.4	-9.003	**0.000***

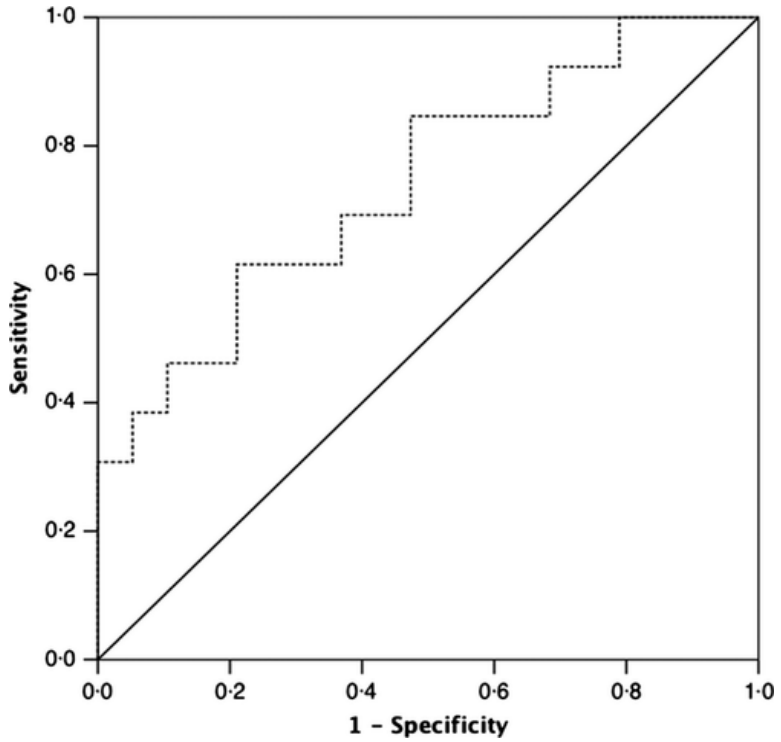

Fig. (1): Receiver operating characteristic (ROC) curve of serum cortisol for prediction of mortality (area under the curve 0.75). A cortisol value of 35 µg/dL or greater is a predictor of increased mortality.

DISCUSSION

Forty-four patients and 20 control subjects were included at this study. The mean age of group (1) was 48.8 ± 14.7 months and ranged between one month and twelve years. The mean age ± SD of group (2) was of 37.9 ± 11.8 months. Our study was different from the study of **Patki et al.,** [8] which stated that the median age of his selected group was 3 months and ranged from one month to five years.The majority of our participants were male (54.5%) while females was (45.5%) . these findings were different from **levy et al.,** [9] who reported his major participants were male represented 61.6% while females were 38.4%. In this study, the laboratory data showed that the mean CRP level was 65.8 ±3.48 mg/L and 58.9 ± 2.44 mg/L in group (1) and (2), respectively. They showed a statistically significant difference (P >0.05). These significant difference can explained by increasing serious infections in critical ill

patients. The mean TLC was 15.6 ± 3.94 x10^9/L and 18.5 ± 4.12 x10^9/L in groups (1) and (2), respectively. They showed a weak significance between the two groups (P = 0.04). these findings were nearly close to **De jonge et al.,** [10] who found mean TLC was 13.2 x10^9/L in his study .The mean serum albumin was 3.16 ± 0.96 g/dl and 4.10 ± 0.45 g/dl in groups (1) and (2), respectively. They showed a statistically significant difference (P = 0.001). These findings were nearly close with **Sandeep et al .,** [11] who reported mean serum albumin was 2.5±0.5g/dl in cases and in controls was 4.3±0.6g/dl the explanation for hypoalbunimia in case group that in critical illness there was imbalance between albumin synthesis and degradation,increase capillary leakage and altered intravascular and tissue albumin distribution.

Both the critically ill children and the control groups showed a statistically non-significant difference between them (P >0.05) as regard temperature, respiratory rate, systolic and diastolic blood pressure. But there was significant difference between two group regarding heart rate.

On studying hormonal parameters, it was found that the mean ACTH at the group (1) was 21.7 ± 6.47 pg/ml and group (2) showed mean of ACTH was11.3 ± 2.14. The mean basal cortisol was 25.8±4.62ug/dl and 9.26 ±1.95 ug/dl in group (1) and (2) respectively.

Our results showed that critically ill children had higher serum total cortisol concentrations compared with controls which is in agreement with findings in critically ill children and adults [2,12,3].

Our results showed 10 children out of 44 (22.7%) of the critically ill children died, by comparing serum cortisol level. These findings were similar to **Osama et al .,** [13] who reported that 23.4 % of his studied group (81 patients) non survived.

It was found that cortisol was significantly higher among non-survivors compared to that of survivors (40.9± 7.4 ug/dl versus 24.8 ± 4.5 ug/dl respectively). These findings were nearly close to **Osama et al.,** [13] who found cortisol among non-survived compared to survived (43.73ug/dl versus 22.8 ug/dl) respectively. But our study was different from **levy et a .,** [9] who found baseline cortisol among survivors was 12.5 ug/dl and 22.5 ug/dl among non survivors respectively .

Also, ACTH was significant higher among non-survivors compared to survivors (29.7 ± 5.3 pg/ml versus 20.9 ± 3.4 pg/ml) respectively. These findings were different from **boonen et al.,** [6] who found low ACTH was significant in non-survived patients, he explained that as there were alternative activators as proinflammatory cytokines which can activate cortisol far from ACTH lead to high cortisol level and suppressed ACTH.

The ROC curve analysis of our findings revealed that a baseline cortisol value of 35 µg/dL or greater is a predictor of increased mortality. Similar results of ROC curve analyses were found by others as well **Vassiliadi et al.,** [14]**. Also Osama et al.,** [13] found by ROC curve analysis that total serum cortisol level of 30 ug/dl had agood discriminative power for mortality .

Therefore, high cortisol levels may reflect the severity of illness. Another possible explanation is that high levels of cortisol may be a result to corticosteroid resistance at the cellular level that can lead to increased risk of mortality in critically ill patients [15,5,9]**.**

CONCLUSIONS

in this study we concluded that high serum cortisol levels in combination with high adrenocorticotrophic hormone concentrations are associated with poor outcome in critically ill children.

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