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CORTISOL IN PEDIATRIC SEPSIS AT HAJI ADAM MALIK GENERAL HOSPITAL

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Abstract : Sepsis as one of the most common stressful conditions in human body. As the way the body adapts to stress, during sepsis the body activates the hypothalamic-pituitary-adrenal (HPA) axis, resulting in a significant increase in cortisol levels. Cortisol has been linked to mortality. Prolonged elevated cortisol may increase the likelihood of developing adrenal insufficiency. Measuring cortisol levels becomes critical to aid clinicians in providing therapy and predicting prognosis. This research was measure cortisol in pediatric sepsis. The research was conducted in the pediatric critical care unit and high care unit at Haji Adam Malik hospital, Medan, North Sumatra, Indonesia from 2021 to 2022. Cortisol was assessed from blood sampling at morning and afternoon. Cortisol has increase in pediatric sepsis.

Keywords **- sepsis, adrenal insufficiency, cortisol**

I. INTRODUCTION

Cortisol is a corticosteroid – a steroid hormone derived from cholesterol that plays a significant function in physical health, including the regulation of blood sugar and blood pressure, as well as stress management [1,2]. Normal cortisol levels are in the range of 10 – 20 mg/day. The levels can rise in the context of stress, trauma, hypoglycemia, and other circumstances requiring cortisol hormone [2-4].

Sepsis is one of the most common stressful conditions in human body. Stress is association with disruptions in the biological systems, which are influenced by neuroendocrine reactions. Septic shock activates the hypothalamic-pituitary-adrenal (HPA) axis, resulting in a significant increase in cortisol levels. This activation of HPA axis is the way the body adapts to stress [5]. In sepsis cases, cortisol levels increase in the body.

Cortisol induces fluid retention by activating mineralocorticoid receptors, which increases blood pressure and myocardial contractility due to potentiation of smooth muscle from catecholamine effects. Cortisol stimulates hepatic angiotensinogen production and increases vascular reactivity causing vasoconstriction, especially with the presence of high cortisol levels [6].

Prolonged elevated cortisol may cause the suppression of HPA axis through negative feedback, which increases the likelihood of developing adrenal insufficiency [7]. Patients with adrenal insufficiency have hemodynamic instability and weak catecholamine response. Early detection of multiorgan dysfunction, including adrenal insufficiency, aids clinicians in providing therapy and predicting prognosis. Measuring cortisol levels is critical in the diagnosis of adrenal insufficiency [8].

Various studies on the increase in cortisol hormone in children with sepsis have been carried out. The hormone level has been linked to mortality. Meanwhile, early detection of individuals at high risk of death still remains a major challenge in the medical field [9]. This research was carried out to observe cortisol in pediatric sepsis.

II. METHODS

This research was a prospective study to assess cortisol in children with sepsis treated in the pediatric intensive care units (PICU) and high care unit (HCU) at Haji Adam Malik hospital, Medan, North Sumatra, Indonesia over a period of eight months, from May 2021 to January 2022

2.1 Research Subject

The research subjects were children aged between 1 month to 18 years old that fulfilled sepsis criteria. Patients receiving long-term steroid therapy and patients with malignancy or suffering from hypothalamic-pituitary-adrenal disorders were not included in the study. The research subjects were gathered through consecutive sampling [10].

2.2 Sample Size

Correlation analysis test was carried out to assess the relation between cortisol The minimum number of sample for correlation analysis was calculated using the following equation.

$$n = \frac{(Z_\alpha + Z_\beta)^2}{[0.5 \ln(\frac{1+r}{1-r})]^2} + 3 \qquad (2.1)$$

Where n was sample size, α was the significance level 5%, in which Zα equaled to 1.96, β was the research power 80 %, in which Zβ equaled to 0.84, and r was the minimum correlation value considered significant equaled to 0.415 [11]. With the minimum 95% confidence interval and 10% addition to aid design error, the minimum number of sample required was 47.

This research involved 47 research subjects. All research subjects have had complete blood tests, blood culture test, blood gas analysis, as well as tests for kidney function, lactate level, hemostasis, and cortisol. Cortisol was carried out within the first 24 hours of patients' treatment in the PICU and HCU. All the patients were monitored during their treatment in the PICU and HCU until they got discharged or died.

2.3 Cortisol

Cortisol was determined according to the immunoassay method in the clinical pathology laboratory at Haji Adam Malik hospital Medan, North Sumatra, Indonesia. Blood samples were taken in the morning at 08.00 and afternoon at 17.00. Cortisol level was recorded as a ration scale milligram per deciliter (mcg/dl).

2.4 Data Analysis

Univariate and bivariate analyses were carried out using a statistical computer software (SPSS). Univariate analysis was conducted to describe the research subjects. Categorical data was presented in frequency and percentage. Numerical data was presented in mean ± standard deviation for normal distribution data, otherwise median (range) for non-normal distribution data. Bivariate analysis was carried out to assess the difference between cortisol and mortality [12].

2.5 Research Ethics

Parental consent was received from all the parents or guardians of the research subjects after a prior explanation about the condition of disease, effects of disease, and patients' involvement to the research. This research has been approved by the Research Ethics Committee of the Faculty of Medicine, Universitas Sumatera Utara (No. 715/KEP/USU/2021).

III. RESULTS

3.1 Research Subject Demographic Characteristic

This study involved 47 child in-patients with sepsis treated in the PICU and HCU of Haji Adam Malik hospital, Medan, North Sumatra, Indonesia. There were 28 (59.6%) male patients and 19 (40.4%) female patients. Over one third (18 patients, 38.3%) were below 12 months old, 13 patients (27.7%) aged twelve years old and above, and the remaining research subjects were between one year old and twelve years old. There were 28 deaths (59.6%) recorded. Table 3.1 shows the characteristic demographic of the research subjects.

Table 3.1: Research subject demographic characteristic

Subject Characteristics	n = 47
Gender, n (%)	
Male	28 (59.6)
Female	19 (40.4)
Age, months, n (%)	
< 12 months	18 (38.3)
12 – 23 months	6 (12.8)
24 – 59 months	3 (6.4)
60 – 143 months	7 (14.9)
≥ 144 months	13 (27.7)
Ventilator, n (%)	
Yes	34 (72.3)
No	13 (27.7)
Outcome, n (%)	
Discharged	19 (40.4)
Died	28 (59.6)

3.2 Research Subject Clinical Characteristic

Tabel 3.2 show clinical characteristic in pediatric sepsis at Haji Adam Malik General Hospital Medan.

Table 3.2: Research subject clinical characteristic

Clinical Characteristics	Mean (SD)	Median (Min – Max)
Temperature, ºC	37,72 (0,73)	37,8 (36,5-39)
HR, x/m	121,96 (29,64)	124 (21-180)
BP Sistolic mmHg	101,91 (17,62)	100 (70-147)
BP Diastolic, mmHg	62,45 (11,8)	60 (45-100)
MAP, mmHg	75,87 (12,89)	75,6 (57-115)
Pupil, n (%)		

Reactive	44 (93,6)	
Non Reactive	3 (6,4)	
Culture, n (%)		
Acinobacter baumanii	4 (8,5)	
Candida parapsilosis	1 (2,1)	
E. Faecium. Dan S. Haemolyticus	1 (2,1)	
Kleibsiella pneumonia	2 (4,3)	
Micrococcus luteus	1 (2,1)	
Pseudomonas aeruginosa	2 4,3)	
Sphingomonas paucimo	1 (2,1)	
Staphylpococcus haemolyticus	1 (2,1)	
Elizabethking	1 (2,1)	
No Growth	33 (70,2)	

3.3 Research Subject Labotatorium Clinical

Tabel 3.3 show clinical laboratorium in pediatric sepsis at Haji Adam Malik General Hospital Medan

Table 3.3: Clinical laboratorium in pediatric sepsis

Laboratorium	Mean (SD)	Median (Min-Max)
Haemoglobin, mg/dL	9,76 (3,27)	9,8 (1,8-18,4)
Leucosytes sel/µl	15,3 (7,06)	15 (2,06-35,82)
Hematocrit, %	29,46 (9,89)	29,1 (6,1-56,4)
Thrombocyte, sel/µl	295,74 (210,49)	295 (3-1123)
Lactat, (SD)	2,11 (2,28)	1,4 (0,4-15)
Glucose ad random, ng/mL	118,11 (67,62)	100 (60-500)
Ureum, mg/dL	42,66 (89,8)	6 (0,2-469)
Creatinin, mg/dL	2,96 (6,05)	0,51 (0,2-26,07)
BUN, mg/dL	37,91 (56,68)	12 (0,35-268)
PT, second	15,82 (3,65)	14,8 (11,4-28,2)
aPTT, second	39,53 (16,24)	37,5 (15,2-120)
pH,	7,3 (7,91)	7,34 (6,8-7,59)
pCO2, mmHg	32,66 (29,31)	28 (6-204)
pO2, mmHg	171 (38,29)	182 (29-212)
HCO3, mEq/L	14,89 (7,12)	16 (1,9-35)
Total CO2, mmHg	16,33 (7,23)	17 (2,3-37,3)
BE	-10,48 (7,9)	-9,6 (-28,7 – 7,2)
SaO2, %	97,68 (11,49)	99,7 (20,8-100)

3.4 Cortisol Level in Pediatric Sepsis

Table 3.4 shows the cortisol level of the research subjects tested in the morning and in the afternoon. The mean cortisol level in the morning was 13.6 mcg/dl, where the median value was 13.2 mcg/dl, ranging from 3.8 mcg/dl to 29 mcg/dl. Whereas in the afternoon, the mean cortisol level was 12.81 mcg/dl, with the median value of 12 mcg/dl, ranging from 2.6 mcg/dl to 28 mcg/dl.

Table 3.4: Cortisol levels of research subjects with sepsis in the morning and afternoon

Variable	n = 47
Cortisol in the morning, mcg/dl	
Mean (SD) Median (Min-Max)	13.6 (6.69) 13,2 (3,8-29)
Cortisol in the afternoon, mcg/dl	
Mean (SD) Median (Min- Max)	12.81 (6.28) 12 (2,6-28)

IV. DISCUSSION

Sepsis is the presence of a systemic inflammatory response syndrome followed by a compensatory anti-inflammatory response syndrome. In this study found that the most age of patients were <9 months or child had not yet experienced puberty. This study reported gender did not affect with sepsis in Pediatric. In the adult population, the humoral immune response in women is higher than in men. Experiments on animals states that the presence of the hormone estrogen can enhance the female immune system and high testosterone has a worse outcome in patients with sepsis. .Ghuman et al also reported no significant difference between sex and child mortality with sepsis in prepubertal and post-puberty children. Because apart from gender, there are other factors such as age, source of infection, and patient comorbidities. [13].

Prolonged use of ventilators in children treated in the PICU is strongly correlated with mortality. The indications for using a ventilator in children treated in the PICU are neurological disorders and respiratory failure. Prolonged use of a ventilator can increase health costs which are more expensive and developing with complications. In this study there were 72.3% of patients who used ventilators and not survived was 59.6% [14].

Leon et al reported factors that had an effect on increasing patient mortality were pupillary reflexes, acidosis, BUN and leukocytes. Leukocytes can be used to determine infection with positive likelihood ratios of 0.87 to 2.43. This study found that leukocyte level of patients treated in the PICU and HCU had above normal. The mortality rate was also reported with 59.6% of patients treated in the PICU and HCU with the outcome being death [15].

Sepsis is caused by an immune response triggered by an infection. Bacteria are the most common cause of infection. However, other infections can be caused by fungi, viruses, or parasites. Sepsis also requires proof of the presence of microorganisms which can be done by examining a gram smear, culture results, or polymerase chain reaction (PCR). However, blood culture results from patients with sepsis are often negative. In the adult population, 28% to 49% of patients with severe sepsis also have negative blood cultures. This study found that 14 people had positive bacterial culture results and the remaining 33 people had negative result [16].

Sepsis is also a condition in which the body experiences stress. . Hypothalamus-pituitary-adrenal axis (HPA) is activated when stress condition. The activation of HPA raises corticotropin releasing hormone (CRH) from the hypothalamus the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary. ACTH release the adrenal glands to produce cortisol [17].

The activation of the HPA axis by sepsis increases the concentration of cortisol which is an important component of adaptation to stress. Cortisol causes fluid retention through activation of mineralcorticoid receptors and increases myocardial contractility and blood pressure through potentiation of the effects of catecholamines on cardiac smooth muscle. At high cortisol concentrations, cortisol increases hepatic synthesis of angiotensinogen and increases vascular reactivation to become a vasoconstrictor. Cortisol functions to maintain the body's homeostasis [18].

In this study, both cortisol levels increased in the morning and afternoon. A different study obtained by Jacob et al stated that total cortisol concentration levels increased in patients admitted to the PICU and became normal later. Free cortisol concentration levels also increased compared to healthy children at the time of admission to the PICU. Menon et al investigated by measuring levels of free cortisol and total cortisol in children with septic shock. From this study it was found that there was a significant correlation between free cortisol and total cortisol ($R2=0.92$, $p<0.001$). The mean total cortisol was 609 nmol/L and free cortisol was 61 nmol/L in children with septic shock. This study implies that many children with septic shock stimulate the HPA axis to increase cortisol production in response to severe critical illness [19].

Elevated cortisol may cause the suppression of HPA axis through negative feedback, which increases the likelihood of developing adrenal insufficiency [7]. In this study, the cortisol level in this research varied where the lowest cortisol level recorded was 3.8 mcg/dl and the highest was 29 mcg/dl. This research was limited by the absence of ACTH stimulation test, which was not enabling the classification of adrenal insufficiency

V. CONCLUSION

Cortisol level increased in child patients with sepsis.Increased cortisol levels in response to the body's adaptation to stress. Cortisol has a role to maintain vascular tone, endothelial integrity, vascular permeability, and modulation of the immune response. Cortisol has been linked to mortality. Prolonged elevated cortisol may increase the likelihood of developing adrenal insufficiency. Measuring cortisol levels becomes critical to aid clinicians in providing therapy and predicting prognosis.

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