Original Article

The Role of Blood Cortisol Levels in the Prognosis for Pediatric Septic Shock

Nguyen The Nguyen Phung, Thi Ngoc Diep Doan, Diep Tuan Tran*

Department of Pediatric, University of Medicine and Pharmacy at Ho Chi Minh City, Ho Chi Minh city 700000, Vietnam.

Abstract

Background: The rate of mortality from septic shock currently remains high in pediatric intensive care units. In this disease, adrenal insufficiency is a commonly occurring problem that also influences prognosis. Diagnosis and treatment are still controversial. In consideration of these issues, we determined the rate of adrenal insufficiency in children suffering from the condition and the role of blood cortisol levels in prognosis. **Materials and Methods:** This prospective, descriptive, analytical study involved 74 septic shock cases at the intensive care unit and emergency department of Children's Hospital 1 in Vietnam. The research was conducted from October 2008 to April 2011. **Results:** Most of the subjects were under 5 years old (81.5%), and 46.8% of them were male. Malnutrition occurred in 14.9% of the patients. The majority were in very serious condition upon admission, all were in decompensated shock, 55.4% had unmeasured blood pressure, 73% were afflicted with disorders of consciousness accompanied by confusion and coma, 46.8% needed to be intubated at admission, and 94.6% exhibited multiorgan dysfunction. The PRISM II of the children averaged at 26.6±10. Adrenal insufficiency rates were 9.5%, 13.5%, and 31.1% at admission, at 6 hours after treatment, and at the 24th hour of intervention, respectively. Such rate was 41.9% overall. Adrenal insufficiency was unrelated to mortality, but the group with blood cortisol levels >340 ng/mL had a higher mortality rate. Among the children, 86.3% had blood cortisol levels >180 ng/mL, and 16.1% children had blood cortisol concentrations <180 ng/mL ($p = 0.018$)—both suffered additionally from disorders involving three or more organs. Blood cortisol concentrations gradually decreased over three times at certain points in the research. No difference in time and number of vasoactive drugs was found between the groups of patients with and without adrenal insufficiency. The former had higher dopamine concentrations in the body ($p = 0.028$). **Conclusion:** The majority of the children were in very serious condition and suffered from decompensated shock, with many of their organs affected. The rate of adrenal insufficiency in the sample was high but unassociated with mortality. Blood cortisol increased at the time of diagnosis and decreased after. The children with adrenal insufficiency had higher levels of dopamine in their system.

Keywords: cortisol, pediatric, sepsis, septic, shock, Vietnam

Introduction

Septic shock is an intense phase of an ongoing process and begins with systemic inflammatory response syndrome (SIRS) that is due to infection, severe sepsis, and septic shock, eventually leading to multiorgan dysfunction. It is one of the major causes of death in both adults and children admitted to intensive care units. Septic shock in pediatric patients is defined as tachycardia (may be absent in a hypothermic patient) with signs of decreased perfusion, including reduced peripheral pulses in comparison with central pulses, altered alertness, flash capillary refill or capillary refill >2 seconds, mottled skin or skin cool to the touch in the extremities, or decreased urine output; hypotension is a sign of late and decompensated shock in children.[1]

In Vietnam, the rate of mortality from septic shock is still very high. From 2003 to 2005, for example, death due to septic shock at Children's Hospital 1 occurred among 75.4% of patients, and from 2000 to 2003, such rate in Children's Hospital 2 amounted to 86.5%. [2, 3] In septic shock among children, a common complication is adrenal insufficiency, with incidences of 17% to 54% across different studies. Adrenal insufficiency is typically treated with

Address for correspondence: Diep Tuan Tran, PhD. MD., Department of Pediatric, University of Medicine and Pharmacy at Ho Chi Minh City, Ho Chi Minh city 700000, Vietnam.
E-mail: DiepTuan@ump.edu.vn

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hydrocortisone, for which the criteria for diagnosis and replacement therapy remain inconsistent. In Canada, this medication is used to address septic shock at a frequency of up to 75%. Steroid therapy, such as hydrocortisone-based intervention, is recommended in cases of catecholamine-resistant shock, abnormality in the hypothalamic-pituitary-adrenal axis, septic shock caused by meningococcus, or corticoid administration because of chronic disease.

The diagnosis of adrenal insufficiency is based on total cortisol or free cortisol in the blood and on response to a corticotropin stimulation test. However, the implementation of the test is inconsistent because a considerable amount of time is spent waiting for results. This challenge highlights the importance of blood cortisol concentration in the diagnosis of adrenal dysfunction in septic shock pathology. Meanwhile, the early identification of multiorgan dysfunction helps clinicians implement appropriate treatment after an initial emergency. Correspondingly, we measured the concentrations of blood cortisol in pediatric septic shock patients to assess adrenal insufficiency and its value in prognosis for the disease.

Materials and Methods

This prospective, descriptive, and analytical study investigated the average concentration and pattern of blood cortisol as well as its role in the prognosis of septic shock patients admitted into the intensive care unit and emergency department of Children's Hospital 1 in Vietnam. All the children admitted to these departments between October 2008 and April 2011 and diagnosed as suffering from septic shock (including circulatory dysfunction plus bacterial infection) were included in the study. The standards for septic shock diagnosis were agreed upon in the International Pediatric Sepsis Consensus Conference, with the following definitions established for sepsis and organ dysfunction in pediatric patients:[4]

1) SIRS is caused by at least two factors, one of which must be an abnormal bodily temperature or an abnormal leukocyte count.
   - Central body temperature: >38.5°C or <36°C
   - Rapid heartbeat above normal by age or slow in children younger than 1 year
   - Rapid breathing by age
   - Leukocyte count increase or decrease by age or more than 10% of immature neutrophils in peripheral blood
2) Blood cultures are positive for bacteria or fungi.

The study excluded children under 2 months of age; those with congenital heart disease or congenital pathologies that affect prognosis, such as cerebral palsy, congenital neuromuscular abnormalities, and endocrine disorders; children with pre-sepsis organ dysfunctions, such as liver and kidney failure; children diagnosed with septic shock and treated at local health care facilities; and children who died before 24 hours of follow-up and contracted shock through other causes.

Total blood cortisol was quantified as 2 mL of blood coagulation. Samples were taken using a Liaison machine (Diasorin, Italy) and sent to Cho Ray Hospital at T0 (time of diagnosis), T6 (6 hours after treatment), and T24 (24 hours after treatment). Adrenal insufficiency was indicated by a total blood cortisol <180 ng/mL and an increase in blood cortisol >340 ng/mL.[5] Pollack's pediatric risk of mortality score II (PRISM II).[5]

Statistical analysis

Data were collected using unified sample records and analyzed using the Statistical Package for the Social Sciences (version 18.0). Descriptive statistics with quantitative variables were calculated as mean±standard deviation, and qualitative variables were determined as frequencies and percentages. Analytical statistics were derived using a comparison of the average values of the quantitative variables in different patient groups via a t-test (normal distribution) and the Mann–Whitney U test (non-normal distribution). The comparison of the qualitative variable ratios through a Chi-square (χ^2) test was corrected using Fisher's exact test. A p value less than 0.05 was considered significant.

Ethical considerations

The study protocols were approved by the Scientific Research Committee of Children's Hospital 1, and the collected data were used only for research purposes. Participation was voluntary and anonymous, with the children's guardians asked to sign informed consent forms prior to enrollment.

Results

The final sample comprised 74 patients, of which 48.6% were male, 39.2% were infants, 45.6% were 1 to 5 years old, and 14.9% were over 5 years old. Among children aged 1 to 5 and more than 5 years in Ho Chi Minh City, malnutrition rates were 14.9% and 44.6%, respectively. Manifestations of SIRS included hyperthermia (56.8%), rapid pulses (93.2%), slow breathing, and apnea (48.6%). All the patients exhibited decreased blood pressure, but this vital sign was unmeasured for 44.6% of the sample. A total of 94.6% suffered from multiorgan dysfunction, and the average PRISM II score of the patients was 26.6±10.

The average cortisol concentrations at T0, T6, and T24 were 698.2±653.3, 517.9±598.2, and 368.6±344.7 ng/mL, respectively. A rate of decreased cortisol <180 ng/mL at the time of diagnosis, T6, and T24 occurred among 9.5%, 13.5%, and 31.1% of the patients, respectively. When cortisol concentrations <180 ng/mL were considered once in every three measurements, 32 children (41.9%) registered as exhibiting levels <180 ng/mL. Of these patients, two had a threefold reduction in quantitative concentrations <180 ng/mL, and four showed decreased concentrations in two measurements.

The PRISM score that separated the survival and fatality groups was 28. A total of 80.6% and 88.4% of the children with PRISM scores >28 and ≤28, respectively, died. The analysis of the correlation between and cortisol indicated that at T24, 83.2% of the children with PRISM scores >28 had cortisol levels >180 ng/mL, and 16.1% exhibited cortisol concentrations ≤180 ng/mL (p = 0.018).

Table 1: The relationship between cortisol concentration and mortality

		Cortisol concentration			
		<180 ng/mL n (%)	**180–340 ng/mL n (%)**	**>340 ng/mL n (%)**	**p value**
T0	Dead	3 (42.9)	4 (23.5)	23 (46.0)	0.26
	Alive	4 (57.1)	13 (76.5)	27 (54.0)	
T6	Dead	5 (50.0)	8 (29.6)	17 (45.9)	0.34
	Alive	5 (50.0)	19 (70.4)	20 (54.1)	
T24	Dead	4 (17.4)	11 (47.8)	15 (53.6)	0.02
	Alive	19 (82.6)	12 (52.2)	13 (46.4)	

Table 2: The relationship between cortisol concentration and vasomotor

	Cortisol concentration		
	<180 ng/mL	**≥180 ng/mL**	**p value**
Catecholamine-resistant shock n (%)	11 (37.9)	18 (62.1)	0.77*
Using ≥3 types of vasomotor (%)	11 (40.7)	16 (59.3)	0.84*
Maximum dopamine dose M±SD	11.7± 3.2	10.1±2.6	0.028†

*: χ^2 test

†: **T-test**

Discussion

All the hospitalized children were in very serious condition, with 30 (40.5%) of them dying after 24 hours of hospitalization. All the patients presented with decompensated shock, 55.4% had unmeasured blood pressure, and 46.8% needed intubation upon hospitalization. The rate of multiorgan dysfunction and the PRISM scores were very high (94.6% and 26.6±10, respectively).

Much progress has been achieved in understanding the pathophysiology of septic shock, and consensus has been reached regarding diagnosis and treatment in an international conference on sepsis and septic shock. Nevertheless, the rate of fatalities from the disease is still high possibly because of the lateness with which a patient is hospitalized (i.e., once the disease had already taken a severe turn). Late hospitalization stems from late identification by family and medical staff—an issue also noted in other research on sepsis and septic shock in Vietnam.[2, 6]

The average cortisol concentration gradually decreased over time, as determined across three measurements. In particular, the proportions of patients with cortisol levels <180 ng/mL at T0, T6, T24 were 9.5%, 13.5%, and 31.1%, respectively. At present, no unified standards exist for the relative and absolute diagnoses of adrenal insufficiency in children. According to Dellinger et al.,[7] the reunification of resuscitation associations in guidelines for the diagnosis and management of sepsis and septic shock sets forth criteria for the absolute diagnosis of adrenal insufficiency in cases of catecholamine-resistant shock under random quantitation without consideration for time in patients with daily cortisol <180 ng/mL (496 nmol/L). Relative adrenal insufficiency is defined on the basis of an adrenocorticotropic hormone (ACTH) stimulation test as manifested by occurrence 30 to 60 minutes later and a cortisol increase ≤90 ng/mL (248 nmol/L). On the basis of this definition, 32 children (41.9%) in this study exhibited a single incidence of quantitative cortisol <80 ng/mL. Two of these patients had decreased cortisol levels, as ascertained in three measurements, and four showed reduced concentrations in two measurements. The study was not contingent upon the implementation of an ACTH stimulation test (In Vietnam, the required drugs were unavailable, and the diagnostic criteria, indications for treatment, and clinical cortisol indications were inconsistent.).

Casartelli, Garcia, Branco, Piva, Einloft, and Tasker stated that the rate of adrenal insufficiency in children with septic shock ranges from 17% to 54%.[8] Although a decrease in corticosteroids is unassociated with death, this deficiency diminishes immune response and the reaction of blood vessels to catecholamines.[9] Pizarro, Troster, Damiani, and Carcillo inquired into the relationship between adrenal insufficiency and catecholamine resistance in 57 children with septic shock in Brazil [10] and the sepsis definitions established during an international conference on sepsis. The authors tested 250 µg of corticotropin as well as cases wherein absolute adrenal insufficiency upon blood cortisol increases to ≤9 µg/dL and blood cortisol levels are <20 µg/dL and relative adrenal insufficiency upon blood cortisol increases to ≤9 µg/dL after testing and blood cortisol concentrations are >20 µg/dL. The authors found an absolute adrenal insufficiency rate of 18% and catecholamine resistance in all the cases. The relative adrenal insufficiency and catecholamine resistance in the current work were 26% and 80%, respectively. All the children without adrenal insufficiency responded to infusion, but those suffering from adrenal insufficiency had a 1.88 higher chance of increased risk of catecholamine resistance. Differences in

catecholamine or dopamine resistance were not recorded (Table 2).

In North India, Valoor, Singhi, and Jayashree conducted a randomized double blind study on 38 children aged 2 months to 12 years and suffering from septic shock.[11] The authors found that low doses of hydrocortisone failed to stimulate response to infusion and that the children needed vasomotor. The researchers administered 5 mg/kg of hydrocortisone per day, divided into four allocations until recovery from shock and then halved and stopped for seven days. The results showed that recovery time in the treatment group was 49.5 hours, whereas that in the normal saline group was 70 hours. Both groups exhibited a low demand for vasomotor and identical mortality rates.

In Australia and New Zealand, up to 60% of resuscitation clinicians increase the use of hydrocortisone for septic shock, whereas in Canada, this rate is 75%. [9] Adrenal insufficiency can cause unresponsiveness to treatment, especially with infusion and vasopressors. In Tran's exploration of adrenal insufficiency in 30 children with septic shock, 30% of the patients had relative adrenal insufficiency and a mortality rate of 56%.[6] Those with adrenal insufficiency also had higher catecholamine resistance.

Studies on sepsis and septic shock in children often showed reduction in cortisol, which corresponds to adrenal insufficiency and increased mortality, especially in meningococcal sepsis cases. In research on 96 children suffering from meningococcal sepsis, Riordan, Thomson, Ratcliffe, Sills, Diver, and Hart found an average cortisol concentration of 385 ng/mL (160–740 ng/mL) in the fatality group and a concentration of 453 ng/mL (160–1860 ng/mL) in the survival group. [12] The authors reported no cases with blood cortisol <50 ng/mL, and two out of three children with concentrations <180 ng/mL died. No association was found among cortisol concentration, shock, and disease severity, but the researchers indicated that the children who died had low cortisol concentrations.

Pizarro, Troster, Damiani, and Carcillo stated that the highest mortality in a group with cortisol >20 µg/mL showed an increase in cortisol levels <9 µg/mL after an ACTH stimulation test. [10] Annane, Sebille, Troche, Raphael, Gajdos, and Bellissant also noted high concentrations in mortality cases and poor response to an ACTH stimulation test. [13] Sam, Corbridge, Mokhlesi, Comellas, and Molitch measured the cortisol levels of more than 100 patients under a 48-hour onset of septic shock and identified a mortality rate of 51%. [14] In 30% of the children with cortisol levels <200 ng/mL, the mortality rate was 53%, and in those with cortisol concentrations ≥450 ng/mL, such rate was 81%. Similarly, we found a higher mortality rate in the group with cortisol concentrations >180 ng/mL (Table 1).

Assessing cortisol using the PRISM II scale, we determined that the children with scores >28 had higher cortisol concentrations than those of the children with scores <28. In a study on 24 children with sepsis and septic shock, Garcia, Milano, Lopez, Valls, and Calvo found an average cortisol level of 243.7 ng/mL and an average ACTH of 135 pg/mL—an increase compared with the levels ascertained in the control group. [15] There were four cases of adrenal metabolic disorders, among whom three had PRISM III scores higher than those of the group with non-adrenal metabolic disorders.

We divided the sample into three cortisol groups: The first had cortisol levels <180 ng/mL, the second had concentrations of 180 to 340 ng/mL, and the third had concentrations >340 ng/mL. In three measurements, the highest rate was exhibited by the >340 ng/mL group, followed by the 180 to 340 ng/mL group and the <180 ng/mL group (Table 1). The greatest incidence of mortality occurred in the >340 ng/mL group (Table 1), with a $p = 0.02$. A high or normal concentration of cortisol in a patient may still result in adrenal metabolic disorders or inadequate adrenal response under "stress" conditions. A corticotropin stimulation test can facilitate the evaluation of adrenal function and the prediction of disease occurrence. A corticotropin stimulation test indicates that despite high concentrations, patients with increased cortisol concentrations <90 ng/mL can use steroids. Relative adrenal insufficiency due to insufficient cortisol response in septic shock. The clinical manifestations of relative adrenal insufficiency are hemodynamic disorders and unresponsiveness to infusion and vasomotor.

Zimmerman asserted that even when cortisol levels increase, relative cortisol deficiency at the site of inflammation still occurs because of decreased cortisol-binding globulin, the activation of 11-hydroxysteroid dehydrogenase, glucocorticoid receptor inhibition, a decrease in receptor affinity with cortisol, and elevated anti-glucocorticoid activity. [16] The body's response to sepsis and septic shock involves the hypothalamic–pituitary–adrenal axis and the sympathetic system. The activation of the aforementioned axis increases the production of the corticotropin-releasing hormone (CRH) and vasopressin by the hypothalamus. CRH stimulates ACTH production from the anterior pituitary gland, which increases cortisol production from the adrenal glands. Cortisol exerts many effects on the metabolic, cardiovascular, and immune systems, thereby maintaining homeostasis in a state of stress.

Few studies have been devoted to steroid use in children. An example is the work of Markovitz, Goodman, Watson, Bertoch, and Zimmerman, who searched for data on steroid use as treatment for severe sepsis. [17] In steroid treatment studies involving 6,693 children, the mortality rates were 30% in the treatment group and 18% in the untreated group. [17] The steroid group stayed in hospital, exhibited vasomotor symptoms, and required longer mechanical ventilation. No evidence has been found on whether prognosis improves with the steroidal treatment of sepsis, although the debate on such intervention is ongoing. Hebbar, Stockwell, Leong, and Fortenberry carried out retrospective studies on 78 children

who were administered a corticotropin stimulation test to diagnose adrenal insufficiency. [18] The results showed high rates of adrenal insufficiency; that is, 56% of absolute adrenal insufficiency, 50% of the relative variant, and 88% of either relative or absolute adrenal insufficiency. Using low-dose hydrocortisone reduced the need for dopamine and norepinephrine doses. More research is needed on indications, subjects, whether an ACTH stimulation test should be performed to guide treatment, whether fludrocortisone should be administered as treatment, and duration of steroid treatment. Furthermore, randomized controlled studies on pediatric patients with septic shock are essential.[7]

Our investigation uncovered no difference in average cortisol concentration between the mortality and survival groups. We found that the group with cortisol levels >340 ng/mL had the highest mortality rate. The results of the present research are similar to those of Bollaert, Fieux, Charpentier, and Lévy,[19] who looked into 82 cases of septic shock, excluding children who died 24 hours prior to treatment. The authors found a 28-day mortality rate of 50% and an average cortisol concentration of 227±10 ng/mL. The multivariate analysis revealed cortisol levels >200 ng/mL and showed that patients with a cortisol increase <90 ng/mL, as determined from the corticotropin stimulation test, exhibited the highest mortality rate. Is the corticotropin stimulation test necessary in the assessment of adrenal status in children with septic shock before steroid administration? Our study does not support the routine use of steroids as treatment for septic shock or steroid treatment based on baseline cortisol concentration.

Conclusion

Cortisol concentrations decreased over three quantitative measurements. The patients with cortisol concentrations >340 ng/mL had the highest mortality rate. The rate of adrenal insufficiency, as determined on the grounds of an international conference on sepsis, was 41.9%.

Conflict of Interest

The authors have no conflicts of interest to declare.

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