



Serum Cortisol Levels in Children with Catecholamine-Dependent Shock – A Prospective Observational Study

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Article History

Received on: 04 Feb 2024
Revised on: 11 Mar 2024
Accepted on: 15 Mar 2024

Keywords

Pediatric,
Shock,
Catecholamine,
Cortisol

Abstract

Pediatric septic shock poses a significant challenge in ICUs worldwide, with high mortality and morbidity rates despite medical advancements. Early recognition and aggressive management are crucial. Resistance to standard therapies in some cases suggests potential adrenal insufficiency, particularly relative adrenal insufficiency (RAI), though research is limited. This study aimed to assess adrenal insufficiency prevalence in pediatric septic shock by evaluating basal serum cortisol levels in 49 children aged 1 month to 12 years admitted to the PICU. Results showed a significant 41% prevalence of adrenal insufficiency, correlating with prolonged critical care needs. Despite increased interventions, mortality rates didn't notably differ between groups. Recognition of adrenal insufficiency is vital due to its association with extended critical care requirements. Further research, including stimulation tests and trials, is needed to distinguish absolute and relative adrenal insufficiency and assess potential benefits of steroid supplementation. This study underscores the importance of comprehensive management strategies incorporating adrenal function assessment in improving outcomes for critically ill children with septic shock.

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eISSN: 0975-7538

DOI: <https://doi.org/>



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INTRODUCTION

In pediatric intensive care units globally, severe sepsis and septic shock present formidable hurdles, leading to elevated mortality and morbidity rates,

a challenge persistent even in developed nations. The key to enhancing results for pediatric patients grappling with septic shock rests in swift identification, vigorous hydration, immediate commencement of the initial antibiotic dosage, and the timely dispensation of suitable inotropic medications.

In the PICU, a subset of children with septic shock presents with fluid and catecholamine-resistant shock, potentially indicating adrenal insufficiency. While absolute adrenal insufficiency is rare, relative adrenal insufficiency (RAI) is more common in pediatric septic shock cases. Limited studies exist in children regarding the prevalence and impact of adrenal insufficiency, particularly

the distinction between absolute and relative forms, which is often determined by basal cortisol (CL) levels. The assessment of adrenal reserve can be conducted using a low-dose adrenocorticotrophic hormone (ACTH) stimulation test.

Current literature in adults suggests that early glucocorticoid treatment improves outcomes, but insufficient research exists for pediatric populations. Various studies use different cortisol level thresholds to define adrenal insufficiency in critically ill patients [1]-[7]. This prospective observational study aims to determine the prevalence of adrenal insufficiency in children with septic shock by measuring basal serum cortisol levels. The study further investigates the association between cortisol levels and clinical outcomes, including the need for inotropic and ventilator support, length of hospital stay, and mortality in these pediatric patients.

SUBJECTS AND METHODOLOGY

This prospective observational study aimed to ascertain the prevalence of adrenal insufficiency, as indicated by reduced serum cortisol levels, among children experiencing fluid-refractory or catecholamine-dependent septic shock. Conducted at the emergency department and pediatric intensive care unit of the Institute of Social Pediatrics, Stanley Medical College, India, the study enrolled 49 children meeting the inclusion criteria after obtaining ethical committee approval and informed consent from parents or legal guardians. Inclusion criteria encompassed children aged 1 month to 12 years admitted with septic shock or developing it during PICU stay, who were reliant on catecholamines. Exclusion criteria included children with inborn errors of metabolism, primary adrenal insufficiency, known hypothalamic-pituitary dysfunction, immunosuppressant or chemotherapeutic usage, recent steroid administration, phenytoin, phenobarbitone, rifampicin intake, or absence of parental consent. SIRS diagnosis required meeting at least two of four criteria, including abnormal temperature or leukocyte count, with sepsis defined as SIRS in the presence of suspected or proven infection. Septic shock involved sepsis coupled with altered consciousness or specific clinical signs like tachypnea, tachycardia, bounding peripheral pulses, or delayed capillary refill,

indicative of compromised perfusion. The study's significance lies in recognizing adrenal insufficiency promptly, crucial for managing septic shock effectively, emphasizing the importance of timely interventions such as aggressive fluid resuscitation, antibiotic administration, and appropriate inotropic support. By elucidating the relationship between adrenal function and septic shock in pediatric patients, this research aims to enhance clinical management strategies, potentially reducing morbidity and mortality rates associated with this critical condition.

In our study, we delineated fluid-refractory shock as a state wherein pediatric patients failed to exhibit improvement following the administration of fluid boluses amounting to 20ml/kg, administered up to five times, or upon the emergence of pulmonary congestion, whichever occurred earlier. We opted for a maximum allowance of five fluid boluses to accommodate children facing acute diarrheal disorders, ensuring thorough consideration of their unique physiological challenges.

Subsequently, catecholamine-dependent shock was defined as the condition wherein children exhibited unresponsiveness to the maximum permissible fluid boluses or displayed manifestations of pulmonary congestion, prompting initiation of inotropic agents. At the time of septic shock diagnosis, comprehensive patient evaluations were conducted, encompassing detailed history-taking, thorough general physical examinations, and systematic assessments, with specific attention paid to cardiopulmonary parameters. All pertinent findings were meticulously recorded in a standardized proforma, facilitating systematic documentation and analysis.

The investigative arm of our study entailed an array of appropriate tests, including complete blood counts, renal and liver function evaluations, urinalysis, and culture sensitivity assessments of blood, sputum, and urine samples, alongside relevant imaging studies. These diagnostic endeavors were meticulously chronicled within the proforma, ensuring a comprehensive overview of each patient's clinical trajectory.

Aligned with established guidelines, our therapeutic interventions were guided by the principles of pediatric emergency medicine and critical care. This encompassed judicious fluid

resuscitation, prompt administration of antibiotics, initiation of inotropic support as warranted, and provision of ventilatory assistance when indicated. The specifics of each therapeutic modality, including the type, dosage, and duration of inotropic support, alongside the timing for weaning off both inotropes and antibiotics, were meticulously documented in the proforma, facilitating precise treatment tracking and outcome assessment.

For the purpose of cortisol level estimation, blood specimens were obtained from children with septic shock demonstrating resistance to fluid therapy upon initiation of inotropic agents. Notably, no strict time frame was imposed for specimen collection, recognizing the loss of diurnal cortisol variation inherent in critically ill pediatric patients. Thus, our study endeavored to unveil insights into the complex interplay between fluid refractoriness, catecholamine dependence, and adrenal function in pediatric septic shock, aiming to enrich the understanding and management of this critical condition.

RESULTS

Regarding the age, number of patients with less than 1 year was 65 % while it was 35 % between 1 – 4. The male : female ratio was 65:35. The diagnosis in the PICU was tables below – table 1

Table 1 Showing the diagnosis with different cortisol levels and the statistical significance

Diagnosis	Low cortisol N=20	Normal cortisol N=29	Significance (P)
Broncho-pneumonia	13	21	
Bronchiolitis	3	2	
Late onset sepsis	2	2	0.421
Acute CNS infection	2	1	
Acute diarrhoeal disease	0	3	

Regarding the cortisol levels, 20 patients had low cortisol level (mean -13.7 µg/dl) while 29 patients had high values. (mean 32.7 µg/dl).

The number of fluid boluses were similar. See table 2. The number of patients where inotropes were used is depicted in Table 3.

Table 2 Showing the number of fluid boluses

No of fluid bolus 20ml/kg	Low cortisol N=20	Normal cortisol N=29	Significance (P)
1	4	0	0.621
2	11	13	
3	5	5	
5	0	1	

Table 3 Showing the need for inotropes with variable cortisol levels

No of inotropes required	Low cortisol N=20	Normal cortisol N=29	Significance(P)
1	15	22	0.602
2	5	7	

The patients with low cortisol have been given more days of inotropes.

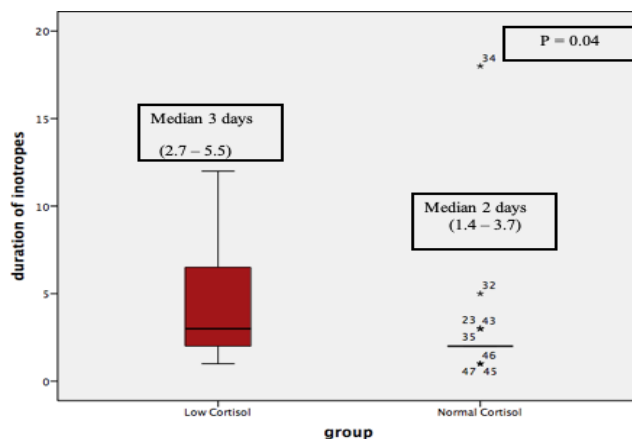


Figure 1 This graph depicts the median days of inotropic support (95% CI) required in each group.

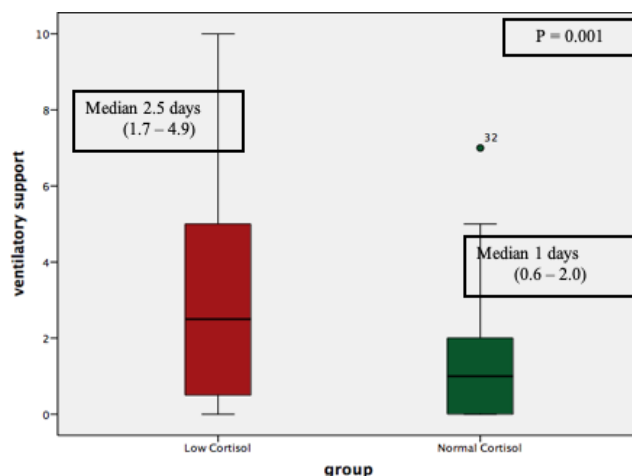


Figure 2 Showing the number of ventilator days with each group

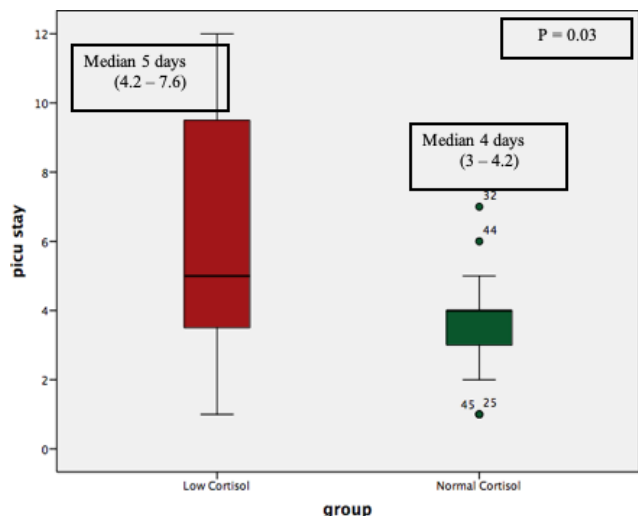


Figure 3 Showing number of PICU days with low and normal cortisol

The number of ventilator dependent days and intensive care stays are also prolonged in patients with low cortisol levels. (figures 2 and 3).

The duration of hospital days is significantly different (more) in patients of low cortisol.

Even though there is a large difference in survival with differing cortisol levels, the change is statistically insignificant.

DISCUSSION

Conducted at the Department of Social Pediatrics, Stanley Medical College, Chennai, the study encompassed 49 predominantly male (67%) pediatric patients under five years old, afflicted by septic shock, with bronchopneumonia emerging as the primary etiology, trailed by bronchiolitis and other infections.

Relative Adrenal Insufficiency (RAI), defined as serum cortisol levels below 18 µg/dl, was prevalent in 41% of cases. Children with RAI experienced prolonged need for inotropic and ventilator support, resulting in extended stays in the Pediatric Intensive Care Unit (PICU) and overall hospitalization. However, mortality rates did not significantly differ between those with RAI and normal cortisol levels.

The study highlighted the critical role of cortisol in stress response, emphasizing its necessity for maintaining hemodynamic stability, metabolic functions, and anti-inflammatory activity. Children with low serum cortisol levels required more extensive support to manage hemodynamic

instability and respiratory complications, leading to prolonged PICU stays. Although mortality rates were similar between groups, the severity of illness upon PICU admission and the virulence of the causative microorganisms likely influenced outcomes. Furthermore, socioeconomic factors affected discharge decisions, with considerations such as transportation and caregiver availability playing significant roles.⁸⁻¹⁵ Most of the studies confirm our findings.

Overall, the study underscores the importance of recognizing RAI in pediatric septic shock cases, as it correlates with prolonged critical care needs. While cortisol deficiency contributes to prolonged illness severity, other factors such as microbial virulence and socioeconomic considerations influence overall outcomes. Hence, comprehensive management strategies must encompass both medical interventions and socioeconomic support to optimize outcomes for pediatric patients with septic shock and RAI

CONCLUSION

In our study, we found a high prevalence of adrenal insufficiency, affecting 41% of our pediatric septic shock population. Pediatric patients exhibiting diminished serum cortisol levels necessitated prolonged reliance on inotropic agents and ventilatory assistance, thus enduring protracted sojourns within the intensive care unit, yet paradoxically, no marked disparities surfaced in overall mortality rates or hospital durations. We concluded that low serum cortisol levels are common in catecholamine-dependent septic shock in children and are associated with prolonged need for critical care. Further investigations, including stimulation tests, and controlled randomized trials are needed to determine the incidence of absolute and relative adrenal insufficiency and to assess the potential benefits of steroid supplementation on morbidity and mortality in these patients.

Ethical Approval

This research was conducted in accordance with guidelines established by the Institutional Animal Ethic Committee (IAEC). Approval number: was obtained from the IAEC prior to the commencement of the study. All procedures involving animals were carried out with care and consideration for their welfare, in compliance with ethical standards and regulations.

Author Contribution

All authors made substantial contributions to the conception, design, acquisition, analysis, or interpretation of data for the work. They were involved in drafting the manuscript or revising it critically for important intellectual content. All authors gave final approval of the version to be published and agreed to be accountable for all aspects of the work, ensuring its accuracy and integrity.

Conflict of Interest

The authors declare no conflict of interest, financial or otherwise.

Funding Support

The authors declare that they have no funding for this study.

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