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Research Article

# Study of Adrenal Insufficiency in Neonatal Septic Shock

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**Received:** January 10, 2023; **Published:** January 25, 2023

## Abstract

**Introduction:** Neonatal sepsis is one of the most common causes of neonatal morbidity and mortality. The prevalence of adrenal insufficiency in neonatal septic shock is not known. Measurement of serum cortisol levels helps in the identification of adrenal insufficiency and its prompt management may decrease mortality due to adrenal insufficiency.

**Objective**: To assess the proportion of adrenal insufficiency in neonatal septic shock.

**Methods**: It is a hospital-based, case series study conducted over 15 months. A total of 35 neonates with septic shock and inotrope support were included and neonates on immune suppressants were excluded. Total serum cortisol levels at the onset of septic shock were measured. Adrenal insufficiency was considered absolute and relative if total serum cortisol levels were less than 6 ug/dl, and 7 to 15 ug/dl respectively.

**Results:** 8 (22.8%) neonates had absolute adrenal insufficiency, 9 (25.71%) neonates had relative adrenal insufficiency, 7 (20%) neonates had normal cortisol levels, and 31 (45.7%) neonates had high serum cortisol levels. 8 Neonates with absolute adrenal insufficiency were given injections of hydrocortisone (1 mg/kg/dose), 7 of them showed clinical improvement in septic shock, and one baby died.

**Conclusion**: Hydrocortisone improved the outcome in neonatal septic shock with adrenal insufficiency. Hence early estimation of cortisol levels and early administration of stress dose of hydrocortisone in adrenal insufficiency in septic shock neonates helps in reducing the mortality.

***Keywords:*** *Adrenal Insufficiency; Cortisol; Hydrocortisone; Neonates; Septic Shock*

## Abbreviation

HPA: Hypothalamic-Pituitary-Adrenal Axis

## Introduction

Neonatal sepsis is the most common cause of neonatal morbidity and mortality in developing countries. The prevalence of adrenal insufficiency in neonatal septic shock is not known. Pathophysiology of shock in newborns is different from children's as it is related to the physiologic transition from fetal to neonatal circulation at birth [1]. Under stressful conditions such as severe sepsis, the absence of an appropriate stimulation of the hypothalamic-pituitary-adrenal axis (HPA) can lead to physiological instability, multiorgan dysfunction, and even death [2]. Metabolism of serum cortisol occurs in the liver and has a half-life of 60 - 90 minutes [3]. In the liver circulating cortisol was reduced to dihydrocortisol, and thereafter to tetrahydrocortisol which was further conjugated to form glucuronic acid. Some part of cortisol is converted to cortisone in the liver which also undergoes reduction and conjugation as cortisol. The water-soluble tetrahydro-glucuronide derivates of cortisol and corticosterone are excreted through the urine. Hence cortisol can be measured in blood, urine, and saliva and adrenal insufficiency can be assessed. Adrenal insufficiency along with decreased vascular responsiveness to catecholamines can contribute to vasopressor-resistant shock [4]. Administration of low-dose steroids in neonatal catecholamine-resistant shock has been found to improve cardiovascular status, further supporting the role of relative adrenal insufficiency [5]. The outcome of neonates with sepsis and septic shock has a poor prognosis and higher mortality rates if unrecognized and if recognized early in a reversible state, the prognosis is good [6].

## Aim of the Study

Hence this study was taken up with the aim to study the serum cortisol levels in neonates with septic shock and with an objective to study the prevalence of clinical adrenal insufficiency and the outcome in comparison with low, normal, and high cortisol levels.

## Materials and Methods

This is a hospital-based case series study conducted over a period of 15 months at the neonatal intensive care unit of a tertiary care teaching hospital in Bagalkot after obtaining ethical clearance. After taking informed written consent, neonates with septic shock were included and those who were on immune suppressants and neonates whose parents refuse to consent were excluded. Clinical and anthropometric parameters and the existence of co-morbidities are recorded in pre-structured proforma. 2 ml of venous blood was collected at the onset of catecholamine-resistant shock (adrenaline, dopamine, and noradrenaline) and total serum cortisol levels are assessed. A stress dose of injection Hydrocortisone (1 mg/kg/dose) was given to neonates with adrenal insufficiency and serum cortisol levels were reassessed within one hour and the outcome of septic shock was measured. Statistical analysis was done using SPSS software19.0. Appropriate statistical tests were applied and a P-value less than 0.05 was considered statistically significant.

### Study variables [7,8]

| Serum cortisol levels | Inference |
|---|---|
| < 6 ug/dl | Absolute adrenal insufficiency |
| 7 to 15 ug/dl | Relative adrenal insufficiency |
| 16 to 23 ug/dl | Normal |
| > 23 ug/dl | High |

## Results

Of the 35 babies with catecholamine-resistant septic shock, 17 (48.56%) neonates had adrenal insufficiency. 8 (22.8%) neonates had serum cortisol levels less than 6 ug/dl, hence considered as having absolute adrenal insufficiency. 9 (25.71%) neonates had serum cor-

tisol levels between 7 to 16 ug/dl, hence considered as having relative adrenal insufficiency. Out of a total of 18 (51.4%) neonates who had serum cortisol levels more than 16 ug/dl, 7 (20%) neonates had normal serum cortisol levels and 11 (31.4%) neonates had higher cortisol levels (Table 1).

| Serum Cortisol Levels | No of cases | Percentage |
|---|---|---|
| Absolute adrenal insufficiency (< 6 ug/dl) | 8 | 22.9 |
| Relative adrenal insufficiency (7 to 15 ug/dl) | 9 | 25.7 |
| Normal (16 - 23 ug/dl) | 7 | 20.0 |
| High (> 23 ug/dl) | 11 | 31.4 |
| Total | 35 | 100.0 |

***Table 1:*** *The proportion of adrenal insufficiency in neonatal septic shock.*

Both low and high serum cortisol levels were found more frequently in term babies and post-term babies compared to preterm babies which are statistically insignificant (Table 2). Among the 35 babies, 5 babies with weight less than 1.49 kg, out of them one had very low (< 6 ug/dl), one had normal cortisol levels, and 3 babies had higher cortisol levels which were statistically insignificant. Out of 12 neonates with weights between 1.5 - 2.49 kgs 4 had low, 3 had relatively low cortisol levels, 2 had normal levels and 3 neonates had higher serum cortisol levels which are statistically insignificant. Out of 18 neonates weighing more than 2.5 kg, 4 had very low cortisol levels, 9 had relatively low levels, 7 had normal and 11 had high serum cortisol levels which are also statistically insignificant (Table 3).

| Gestational Age | Serum cortisol levels | | | | Total |
|---|---|---|---|---|---|
| | < 6 ug/dl | 7 to 15 ug/dl | 16 - 23 ug/dl | > 23 ug/dl | |
| < 37 wks. | 0 | 1 | 0 | 2 | 3 |
| ≥ 37 wks. to < 40 wks. | 2 | 2 | 2 | 3 | 9 |
| ≥ 42 wks. | 6 | 6 | 5 | 6 | 23 |
| Total | 8 | 9 | 7 | 11 | 35 |
| Chi-Square test P < 0.813, Not Significant. | | | | | |

***Table 2:*** *Association between serum cortisol with gestational age.*

| Weight (Kgs) | Serum cortisol levels | | | | |
|---|---|---|---|---|---|
| | < 6 ug/dl | 7 to 15 ug/dl | 16 - 23 ug/dl | > 23 ug/dl | Total |
| 1.0 - 1.49 | 0 | 1 | 1 | 3 | 5 |
| 1.5 - 2.49 | 4 | 3 | 2 | 3 | 12 |
| ≥ 2.5 | 4 | 5 | 4 | 5 | 18 |
| Total | 8 | 9 | 7 | 11 | 35 |
| Chi-Square test P < 0.749, Not Significant | | | | | |

***Table 3:*** *Association between serum cortisol and weight.*

There was no association between serum cortisol levels in neonatal septic shock with maternal risk factors and type of sepsis (Table 4). Among the 20 neonates who were discharged to home, 7 had very low (< 6 ug/dl) serum cortisol levels, 7 had relatively low (7 to 15 ug/dl), 2 had normal (16 - 23 ug/dl) serum cortisol levels, and 2 had very high serum cortisol levels. Out of 15 neonates who died, 1 neonate had very low cortisol levels, 2 had relatively low cortisol levels, 5 had normal cortisol levels, and 7 had higher serum cortisol levels which were statistically significant, showing higher serum cortisol levels had higher mortality and morbidity (Table 5). Out of 8 neonates who received stress dose hydrocortisone, 7 neonates survived and one died. Out of 27 neonates who did not receive hydrocortisone, 14 died and 13 neonates survived which is statistically significant (Table 6).

| | Serum cortisol levels | | | | Chi-Square test | |
|---|---|---|---|---|---|---|
| **Risk factors** | **< 6 ug/dl** | **7 to 15 ug/dl** | **16 - 23 ug/dl** | **> 23 ug/dl** | **P value** | **Significance** |
| Rh-Negative | 1 | 0 | 0 | 1 | 0.596 | NS |
| Fever | 0 | 2 | 1 | 0 | 0.239 | NS |
| Anaemia | 5 | 4 | 5 | 6 | 0.729 | NS |
| PROM | 2 | 3 | 0 | 1 | 0.266 | NS |
| Oligohydramnios | 4 | 3 | 4 | 4 | 0.736 | NS |
| Bad Obstetric history | 2 | 0 | 0 | 0 | 0.067 | NS |
| Previous LSCS | 1 | 0 | 2 | 3 | 0.331 | NS |
| Feto-placental insufficiency | 1 | 0 | 2 | 1 | 0.353 | NS |
| Fetal distress | 4 | 8 | 6 | 6 | 0.175 | NS |
| Prematurity | 2 | 4 | 0 | 6 | 0.095 | NS |
| IUGR | 1 | 0 | 1 | 0 | 0.415 | NS |

***Table 4:*** *Association between serum cortisol levels and maternal risk factors.*

| | Serum cortisol levels | | | | Total |
|---|---|---|---|---|---|
| **Outcome** | **< 6 ug/dl** | **7 to 15 ug/dl** | **16 - 23 ug/dl** | **> 23 ug/dl** | |
| Discharge | 7 | 7 | 2 | 4 | 20 |
| Death | 1 | 2 | 5 | 7 | 15 |
| Total | 8 | 9 | 7 | 11 | 35 |
| Chi-Square test P < 0.031, Significant | | | | | |

***Table 5:*** *Association between serum cortisol levels and outcome.*

| **Outcome** | **Hydrocortisone** | | **Total** |
|---|---|---|---|
| | **No** | **Yes** | |
| Discharge | 13 | 7 | 20 |
| Death | 14 | 1 | 15 |
| Total | 27 | 8 | 35 |
| Fisher's Exact test P < 0.04, Significant | | | |

***Table 6:*** *Association between hydrocortisone and outcome.*

## Discussion

Neonatal septic shock is treated with fluid challenge and vasopressors. Once the HPA axis is activated, simultaneously an increase in the production of cortisol is highly essential for survival [9]. Cortisol being a vital hormone helps in the maintenance of vascular tone, permeability, endothelial integrity, and the distribution of total body water within the vascular compartments [10]. Also, it has a significant role in the maintenance of cardiovascular homeostasis during acute stress. So, Serum cortisol levels should be assessed. The release of cortisol is regulated by a negative feedback mechanism that helps in the improvement of neonates [11]. So, there were many studies in which hydrocortisone was used in neonatal septic shock, once a fluid challenge and vasopressor resuscitation are futile and in whom plasma cortisol levels are not present at appropriate levels [12]. Glucocorticoids have numerous beneficial effects in the treatment of severe sepsis. In a study, Schumer demonstrated that treatment with dexamethasone or methylprednisolone improved patients' survival in severe sepsis [12]. As a result, large well-designed randomized controlled studies were performed to find out whether the corticosteroid treatment has any benefit in the treatment of severe sepsis or septic shock [13]. Later in several meta-analyses, it was concluded that high-dose corticosteroids should not be used in the treatment of severe sepsis or septic shock [14].

In our study, out of 35 neonates, 8 neonates had cortisol levels below 6 ug/dl, 9 (25.71%) neonates had serum cortisol levels between 7 to 16 ug/dl, 7 neonates had cortisol levels between 17 - 23 ug/dl, and 11 neonates had high serum cortisol levels. On the contrary, Erika Fernandez., *et al*. [8] study done on 32 neonates showed cortisol values of < 15 mcg/dl in 18 (56%) neonates. In all, 21 infants were treated with hydrocortisone of whom 13 had cortisol values < 15 mcg/dl.

In our study, there was no association between the level of serum cortisol and the weight of the neonate. A similar observation was found in the study done by Baker C F W., *et al*. [15] who conducted an observational study on 117 infants and concluded that serum cortisol concentrations showed no correlation with the weight of the neonates.

In our study, it was found that there is no correlation between serum cortisol levels and the gestational age of the baby similar to the study conducted by Baker CFW., *et al* [15]. On the contrary, Susan M., *et al*. [16] showed an inverse relationship between cortisol levels and gestational age, with the youngest neonates having the highest cortisol levels.

In our study, early stress dose hydrocortisone given at the onset of neonatal septic shock showed significant clinical improvement and survival. Shaban., *et al*. [17] conducted a study that showed that hydrocortisone therapy improved the state of vasopressor resistance hypotension leading to a better clinical outcome**.** Tantivit P., *et al*. [18] conducted a study that showed improved blood pressure and stabilized term neonates with refractory hypotension.

Our study shows that low serum cortisol with absolute adrenal insufficiency had good clinical outcomes after hydrocortisone dose and high cortisol levels have high morbidity and mortality which is statistically significant whereas normal levels do not show statistical significance. Similarly, Sam S., *et al*. [19] conducted a prospective observational study that concluded that low and high cortisol levels are associated with increased sepsis and mortality. This study showed that one-fourth of neonates with septic shock had absolute adrenal insufficiency at the onset of shock and nearly 30% of neonates with septic shock may have relative adrenal insufficiency. Researchers have explored the biological mechanisms of septic shock for potential interventions [20]. Due to their interactions with immune responses and corticosteroids could act as prognostic guidelines [21]. A stress dose of hydrocortisone helps in reversal of adrenal insufficiency and may change the course of illness i.e. possible improvement in hemodynamic impairment [22]. While studying neonatal shock, adrenal insufficiency was not observed in non-septic critically ill neonates. Therefore, the pathophysiology of adrenocortical dysfunction in septic shock is likely to differ from non-septic aetiologies of shock [23].

## Conclusion

Hydrocortisone improved outcomes in neonatal septic shock with adrenal insufficiency. Hence early estimation of cortisol levels and early administration of stress dose of hydrocortisone in adrenal insufficiency in septic shock neonates helps in reducing the mortality.

## Conflict of Interest

None.

## Bibliography

1. Economou G., *et al*. "Cortisol secretion in stressed babies during the neonatal period". *Hormone Research* 40.5-6 (1993): 217-221.
2. Soliman Ashraf T., *et al*. "Circulating adrenocorticotropic hormone (ACTH) and cortisol concentrations in normal, appropriate-for-gestational-age newborns versus those with sepsis and respiratory distress: Cortisol response to low-dose and standard-dose ACTH tests". *Metabolism: Clinical and Experimental* 53.2 (2004): 209-214.
3. Reimondo Giuseppe., *et al*. "Evaluation of the effectiveness of midnight serum cortisol in the diagnostic procedures for Cushing's syndrome". *European Journal of Endocrinology* 153.6 (2005): 803-809.
4. Higgins S., *et al*. "Hydrocortisone for hypotension and vasopressor dependence in preterm neonates: a meta-analysis". *Journal of Perinatology: Official Journal of the California Perinatal Association* 30.6 (2010): 373-378.
5. Singh Yogen., *et al*. "Advances in Diagnosis and Management of Hemodynamic Instability in Neonatal Shock". *Frontiers in Pediatrics* 6.2 (2018).
6. Osborn David A., *et al*. "Left ventricular contractility in extremely premature infants in the first day and response to inotropes". *Pediatric Research* 61.3 (2007): 335-340.
7. Sari Fatma Nur., *et al*. "Baseline and stimulated cortisol levels in preterm infants: is there any clinical relevance?". *Hormone Research in Paediatrics* 77.1 (2012): 12-18.
8. Fernandez Erika., *et al*. "Prevalence of low cortisol values in term and near-term infants with vasopressor-resistant hypotension". *Journal of Perinatology: Official Journal of the California Perinatal Association* 25.2 (2005): 114-118.
9. Schein RM., *et al*. "Plasma cortisol levels in patients with septic shock". *Critical Care Medicine* 18.3 (1990): 259-263.
10. Melby JC and WW Spink. "Comparative studies on adrenal cortical function and cortisol metabolism in healthy adults and in patients with shock due to infection". *The Journal of Clinical Investigation* 37.12 (1958): 1791-1798.
11. Finlay WE and JI McKee. "Serum cortisol levels in severely stressed patients". *Lancet* 1.8286 (1982): 1414-1415.
12. Lamberts SW., *et al*. "Corticosteroid therapy in severe illness". *The New England Journal of Medicine* 337.18 (1997): 1285-1292.
13. Schumer W. "Steroids in the treatment of clinical septic shock". *Annals of Surgery* 184.3 (1976): 333-341.
14. Lefering R and EA Neugebauer. "Steroid controversy in sepsis and septic shock: a meta-analysis". *Critical Care Medicine* 23.7 (1995): 1294-1303.

15. Baker CFW., *et al*. "Hydrocortisone administration for the treatment of refractory hypotension in critically ill newborns". *Journal of Perinatology: Official Journal of the California Perinatal Association* 28.6 (2008): 412-419.

16. Scott SM and KL Watterberg. "Effect of gestational age, postnatal age, and illness on plasma cortisol concentrations in premature infants". *Pediatric Research* 37.1 (1995): 112-116.

17. Deraz - Submitted for Partial Fulfillment of Master Degree (2018).

18. Tantivit P., *et al*. "Low serum cortisol in term newborns with refractory hypotension". *Journal of Perinatology: Official Journal of the California Perinatal Association* 19.5 (1999): 352-357.

19. Sam Susan., *et al*. "Cortisol levels and mortality in severe sepsis". *Clinical Endocrinology* 60.1 (2004): 29-35.

20. Das BK., *et al*. "Serum cortisol and thyroid hormone levels in neonates with sepsis". *Indian Journal of Pediatrics* 69.8 (2002): 663-665.

21. Fernandez EF., *et al*. "ACTH and cortisol response to critical illness in term and late preterm newborns". *Journal of Perinatology: Official Journal of the California Perinatal Association* 28.12 (2008): 797-802.

22. Clyman Ronald I., *et al*. "Hypotension following patent ductus arteriosus ligation: the role of adrenal hormones". *The Journal of Pediatrics* 164.6 (2014): 1449-1455.

23. Pizarro Cristiane F., *et al*. "Absolute and relative adrenal insufficiency in children with septic shock". *Critical Care Medicine* 33.4 (2005): 855-859.

**Volume 12 Issue 2 February 2023**