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EFFECT OF CORTICOSTEROID SUPPLEMENTATION ON ADRENAL SUPPRESSION AND SURVIVAL IN PATIENTS WITH SEPSIS

Dr Ranjita Mohanty[1], Dr Dillip Kumar Das[2], Dr Santosh Kumar Sahu[3], Dr Bhargabi Mallik[4], Dr. Rajesh Kumar Sahu[5]

[1]Associate Professor, Department of Anaesthesiology, Shri Jagannath Medical College, Puri

[2]Assistant Professor, Department of Pediatrics. S.C.B Medical College, Cuttack

[3]Senior Resident, Department of Anaesthesiology. S.C.B Medical College, Cuttack

[4]Senior Resident, Department of Anaesthesiology. S.C.B Medical College, Cuttack

[5]Assistant Prof. Department of Anaesthesiology, Jajati Keshari Medical College, Jajpur

Corresponding Author:

Dr Bhargabi Mallik. Senior Resident, Department of Anaesthesiology. S.C.B Medical College, Cuttack, Odisha

Abstract

Aim: Our aim was to assess the incidence of adrenal insufficiency in critically ill patients with septic shock admitted to a tertiary care ICU and to assess the effectiveness of hydrocortisone in these patients in relation to mortality of patient and development of septic shock.

Methods: Serum cortisol was measured in 126 patients with sepsis. Patients with decreased cortisol level were divided in to two groups.(group A and B). Group A received 50mg of hydrocortisone 6hourly and group B was given matching placebo. At day 7 serum cortisol level was estimated for both group A and group B. The result was calculated and compared in relation to incidence of adrenal insufficiency, development of septic shock, effect on total leucocyte count and survival at 28 day.

Results: The incidence of adrenal insufficiency in patients with sepsis in our study was 46 out of

126 patients i.e, 36 %. After supplementation of corticosteroid for 7 days the mean value of serum cortisol of group A was 45.37±8.34 µg/dl and group B was 28.37±6.97 µg/dl with *p* value<0.001. So there was highly significant increase in serum cortisol level in group A as compared to group B. At day 7 , in group A, 21% developed septic shock, where as in group B, 34 % developed septic shock. Mortality rate of the patients in group A was 17 % and 21 % in group B at 28th day.

Conclusions: Hydrocortisone supplementation in critically ill patients with low random basal serum cortisol level with sepsis does not significantly improve the overall survival.

Keywords- Adrenal sufficiency, sepsis, Indian population, corticosteroid

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Introduction

Sepsis is a life-threatening illness, where there is a systemic and dysregulated host response to an infection. The presentation may range from non-specific symptoms to severe signs with evidence of multi-organ dysfunction and septic shock.[1] The data from the western world reveals an incidence of septic shock to be 8.2 per 100 intensive care admissions, with a mortality of 55- 62.1% . Septic shock remains the most common cause of death in the ICU with a mortality rate of 30-50% despite conventional treatment methods and effective antibiotic therapy.[2] This reflects the need for further research in management of septic shock with early goal directed and a more targeted therapy. The role of steroids in the treatment of septic shock was first talked about when warehouse documented a case of suprarenal apoplexy in 1915.[3]Cahalane et al documented adrenal hemorrhage in a severe meningococcal septicemia patient and postulated that the adrenal hemorrhage caused an acute addisonian crisis resulting in circulatory collapse and mortality.[4] This observation prompted further studies of glucocorticoid therapy in the treatment of septic shock but the results were inconsistent and resulted in increased mortality in some studies.[5,6,7] The role of Hypothalamo-Pituitary-Adrenal axis in septic shock patients was brought to light with studies of Breigel et al [8] and Annane D et al [9] when they reported high rates of relative adrenal insufficiency in septicemia patients and a increase in overall survival with glucocorticoid replacement in those patients. There is very limited data on the incidence of adrenal insufficiency in Indian patients with septic shock.[10] As the risk factors, source of sepsis and the organisms responsible for sepsis are all different, it becomes necessary to find the real incidence of adrenal insufficiency in Indian population so that early steroid supplementation can be done to reduce septic shock related mortality. The primary objective of this study was to estimate the incidence of adrenal insufficiency in critically ill patients with sepsis, as measured by random serum cortisol levels. The secondary objectives were to evaluate the impact of such dysfunction, and eventually to predict the usefulness of serum cortisol testing and the effectiveness of hydrocortisone in these patients in relation to mortality of patient and development of septic shock.

Methods

After approval from the Institutional Ethical Committee, this prospective randomized controlled study was conducted at ICU of a tertiary care hospital. Written and informed consent was taken from all the patients.Inclusion criteria includes 1. Patients with evidence of Sepsis,2. Patients of both sexes,3. Serum Albumin > 2.5 g/dL.Exclusion criteria were patients with a known disease involving the HPA axis**,** patients already on some form of glucocorticoid treatment**,** patients with Multi Organ Dysfunction Syndrome (MODS) and patients with established septic shock on inotropic support. Evidence of sepsis was defined as patients satisfying at least any two of the Systemic Inflammatory Response Syndrome (SIRS) criteria and having evidence of infection - either positive bacterial cultures or elevated Procalcitonin (PCT)>2 ng/mL. PCT levels <0.5 ng/mL is considered normal, which was determined in many cases by functional sensitivity of early assays, whereas levels >10 ng/mL are considered significantly elevated. Serum

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concentrations between 2 to 10 ng/mL are considered suggestive of sepsis, whereas PCT concentrations between 0.5 to 2 ng/mL indicate the possibility of sepsis but do not rule out other causes of elevated PCT.

ACCP/SCCM CONSENSUS DEFINITIONS[11]

Systemic Inflammatory Response Syndrome (SIRS) Criteria

1. Temperature > 38.3°C or < 36°C
2. Heart rate > 90 beats/min
3. Respiratory rate > 20 breaths/min or PaCO2 < 32 mmHg (< 4.3 kPa)
4. WBC count > 12000 cells/mm3 or < 4000 cells/mm3 or > 10% immature (band) form

Any two of the above criteria must be satisfied to be labeled as to have SIRS. Sepsis is a documented infection along with any two of the SIRS criteria. Severe Sepsis is sepsis associated with organ dysfunction, including, but not limited to, acute oliguria (urine output < 0.5 mL/kg/hr for at least 2hours despite adequate fluid resuscitation), arterial hypoxemia (PaO2/FiO2< 300), coagulation abnormalities (INR>1.5 or aPTT>60 sec), or an acute alteration in mental status. Septic Shock is sepsis with hypotension, despite adequate fluid resuscitation, along with the presence of perfusion abnormalities (hyperlactatemia > 1 mmol/L and decreased capillary refill or mottling).Serum cortisol levels was measured for all patients satisfying the inclusion criteria, at the time of inclusion in the study at day 1.Blood pressure, respiratory rate and temperature of all the patients included in the study was recorded at day 1.Those patients having decreased serum cortisol level was randomly divided into 2 groups – group A and group B.Group A received 50mg of hydrocortisone 6hourly and group B was given matching placebo.At day 7 serum cortisol level was estimated for both group A and group B. The result was calculated and compared in relation to development of septic shock, effect on total WBC count and survival at 28 day/death.

Serum Cortisol Testing

The cortisol level measured by immunoassay in this study was 'Total' serum cortisol which included both free cortisol and the cortisol bound to cortisol binding globulin (CBG) and albumin. This value is dependent on the serum albumin levels, a surrogate for cortisol binding globulin. Hence only patients with a serum albumin >2.5 g/dl were included in this study. A total cortisol value of <20 µg/dL was considered sub-normal.There is no demonstrable circadian rhythm in serum cortisol levels in critically ill patients due to altered HPA axis. So the samples for serum cortisol testing was drawn randomly at any time of the day. All the observed data was tabulated and statistically analyzed and compared between the two groups.

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Statistical software: The Statistical software namely SPSS 22.0 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc**.** Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements was presented as Mean ± SD and results on categorical measurements were presented in number (%).Study population is normally distributed and randomization was done using computer generated 1:1sequence. Student t test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups on metric parameters. Leven's test for homogeneity of variance has been performed to assess the homogeneity of variance ,Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups, Non-parametric setting for Qualitative data analysis. P value of less than 0.05 was taken as statically significant and less than 0.001 was taken as highly significant.

Results

A total of 126 symptomatic patients either sex aged were found positive for sepsis and were included in this study. Random serum cortisol level was estimated in all these patients at the day of admission. Out of these 126 patients, adrenal insufficiency is found in 46 patients (males=25 and females=21). These 46 patients were randomized to two groups : Group A and Group B. Group A received 50 mg of hydrocortisone 6 hourly and group B was given matching placebo. At day 7 serum cortisol level was estimated for both group A and group B.

Fig1: Incidence of adrenal suppression

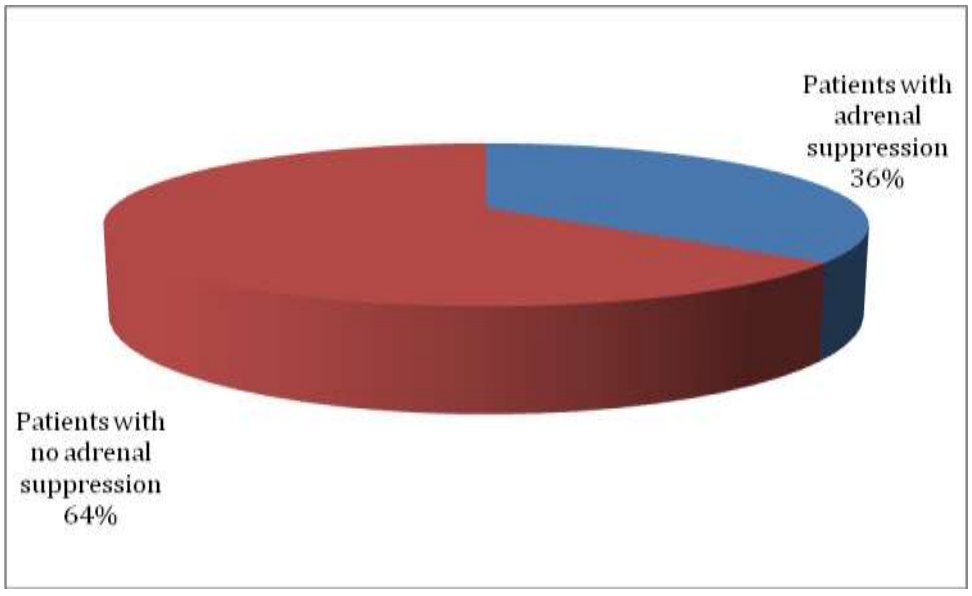

Fig 2-Development of Septic Shock in patients in the two groups at day 7

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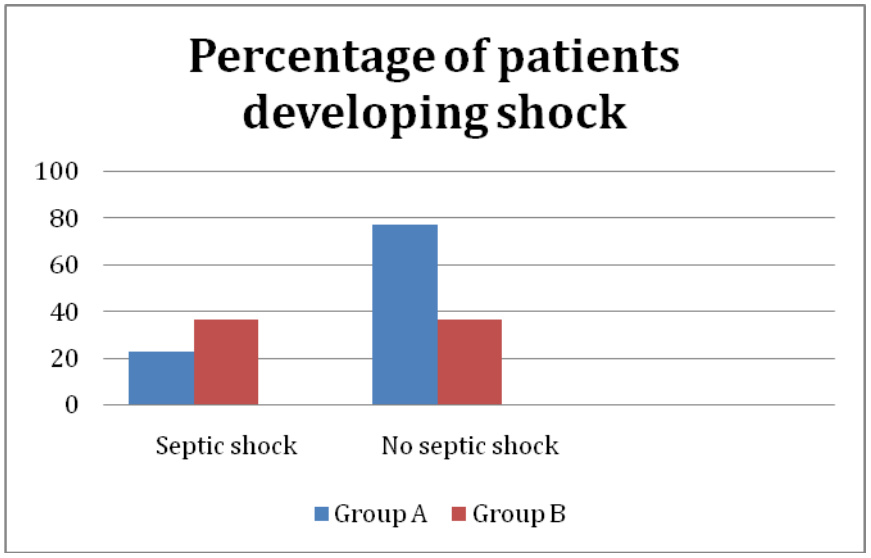

The incidence of development of septic shock and survival at 28 day/death was recorded. In both the groups, empirical broad spectrum antibiotics were started soon after recruitment in the study after sending the samples for bacterial culture and sensitivity. The incidence of adrenal insufficiency in patients with sepsis in our study was 46 out of 126 patients i.e. 36 %. (fig 1)

Table 1 - Serum Cortisol (µg/dl)-Comparison of patients studied in two groups

Serum Cortisol (µg/dl)	**Group A (Mean ± SD)**	**Group B (Mean ± SD**	P value
At Day 1	12.38±2.39	11.76±6.99	0.351
At Day 7	45.37±8.34	28.37±6.97	<0.001

The mean value of serum cortisol at day 1 in group A was 12.38±2.39 µg/dl and group B was 11.76±6.99 µg/dl. So both these groups were comparable with respect to serum cortisol level at day 1.After exogenous supplementation of corticosteroid for 7 days the mean value of serum cortisol of group A was 45.37±8.34 µg/dl and group B was 28.37±6.97 µg/dl with P value <0.001. So there was significant increase in serum cortisol level in group A as compared to group B with *p* value = < 0.001.(table 1) At day 7 in group A, 5 out of 23 patients i.e, 21 % there was development septic shock. Whereas in group B, 8 out of 23 patients i.e, 34% went into septic shock. There was no significant difference observed between group A and group B with respect to development of septic shock.(fig 2)Mortality rate of the patients in group A was 17 % (4 out of 23) and group B was 21 % (5 out of 23). There was no significant difference between two groups with respect overall survival estimated at day 28.(fig 3)

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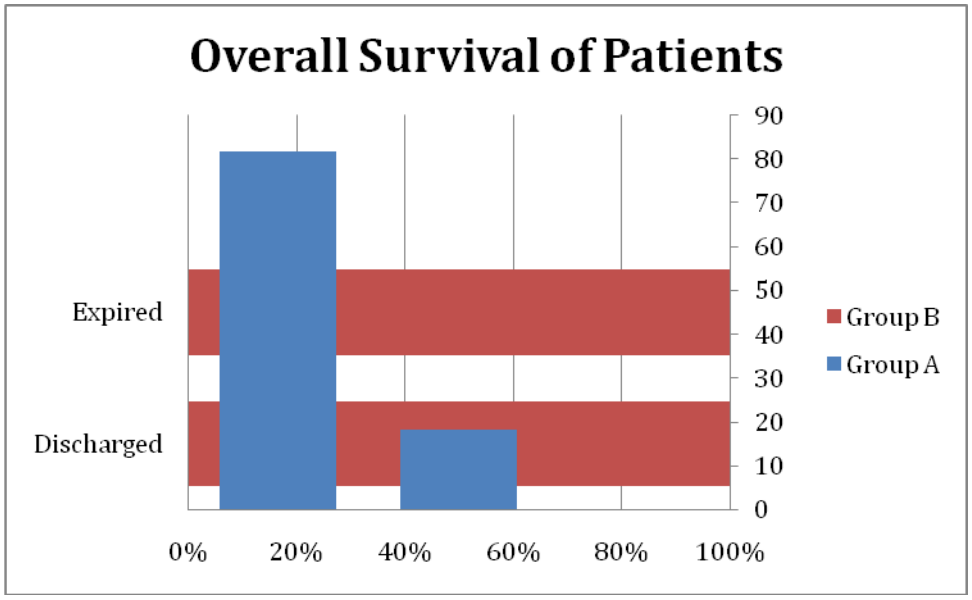

Fig 3-Overall survival of patients studied in two groups at day 28

Discussion

The incidence of adrenal insufficiency were varied greatly in different studies. Suresh et al[12] have found, incidence of adrenal insufficiency in septic shock was 42 % in their study and has also found that basal serum cortisol level was higher in Indian population as compared to western data which is in agreement with our study. Shenker et al[13] have found the incidence of 59% adrenal insufficiency in patients with sepsis and cited that, the diagnosis of adrenal insufficiency presents significant challenges in the critical care setting. The revival of steroid therapy in sepsis based on a theory which is centered on the supplementation of low dose cortisol to substitute a lack of endogenous steroid activity in phases of severe stress. The pathophysiological mechanism is currently discussed as CIRCI: critical illness related corticosteroid insufficiency.[14] Wu et al.[15] concluded that the majority of acutely ill patients who remained in a critical condition had decreased serum cortisol levels. Depressed cortisol levels at follow up may lead to worse clinical outcomes. They proposed that repeated adrenal function testing be conducted in patients with prolonged critical illness. Mani RK[16] opined that relative adrenal insufficiency existed in Indian patients and that there was a basis to use low dose corticosteroids in septic shock. Annane et al[17] has done a trial of 300 patients with septic shock, in which short corticotropin test was done, followed by a seven-day treatment of 50 mg bolus hydrocortisone every 6 hours supplemented by daily fludrocortisone, or placebo. This study showed a survival benefit which contradicts our study.However Gordon Bernard et al [18] concluded that convincing proof that corticosteroids are useful pharmacologic agents in the treatment of severe sepsis remained elusive which was similar to our study. Prigent et al[19] also observed that the diagnosis of adrenal failure in the critically ill remained a challenge and its criteria need to be improved. While the use of high-dose corticoid treatment in sepsis was not justified, replacement therapy by glucocorticoids could improve outcomes in patients in septic shock. Surviving Sepsis Campaign (SSC)[20] recommended in 2016 that low-dose hydrocortisone should not be used as a routine therapy in septic shock if adequate fluid resuscitation and vasopressor therapy can maintain hemodynamic

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stability which is similar to our study.In a study by Sprung et al.[21] the members of the Corticosteroid Therapy of Septic Shock (CORTICUS) study group, concluded that hydrocortisone did not improve survival or reversal of shock in patients with septic shock, which is similar to our study. In a study by Venkatesh B et al[22] (ADRENAL study),they investigated the use of hydrocortisone 200 mg per day in septic shock. They did not found any differences in death from any cause at 90 days after start of the intervention. But they found improvements in morbidity of patients treated with hydrocortisone. Patients treated with hydrocortisone had a shorter time on vasopressor therapy, shorter time on mechanical ventilation and a shorter stay in the ICU. But there was no difference in parameters like 28-day mortality, recurrence of shock, renal replacement therapy, bacteremia or fungemia, and length of hospital stay. Keh et al [23] tested hydrocortisone therapy in patients with severe sepsis and concluded that, use of hydrocortisone did not reduce the development of septic shock within 14 days. Yildiz et al.[24] concluded that there was a trend (that did not reach significance) towards a decrease in the mortality rates of the patients with sepsis who received physiological-dose steroid therapy. The above studies were in agreement with our study. In contrast to our study, Rady et al.[25] concluded that corticosteroids increased the risk for death or disability in critical illness. Hospital-acquired infections, metabolic and neuromuscular sequels of critical illness may be exacerbated by corticosteroids. Careful appraisal of the indications for use of corticosteroids was necessary to balance the benefits and risks from exposure in acute critical illness. Further large scale studies are required to establish this observation

Conclusion

We concluded that the incidence of adrenal insufficiency in critically ill patients with sepsis in our set up is 36 %.The increase in serum cortisol level after corticosteroid supplementation has no role in prevention of development of septic shock. Hydrocortisone supplementation in critically ill patients with low random basal serum cortisol level with sepsis does not significantly improve the overall survival.

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