

Subclinical hypocortisolemia in patients with sepsis in a medical intensive care unit in India (The SHIPS Study)

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Abstract

Objectives: (1) To determine the prevalence of relative adrenal insufficiency in critically ill patients in shock requiring vasopressors for more than 24 hrs, to maintain a mean arterial pressure of 70 mm of Hg. (2) To identify possible risk factors (markers) of a poor cortisol response. **Methodology:** A prospective analysis of 49 critically ill vasopressor dependant patients was performed. A 1 mcg of Synacthen stimulation test was performed and the cortisol response was assessed at 30' and 60'. The criterion of minimum increment in the cortisol response of 9 mcg/dl was used to identify those with relative adrenal insufficiency. The patients were followed up until the time of discharge from hospital. Survival and morbidity indices were the final outcome measures assessed. **Results:** The prevalence of relative adrenal insufficiency in this study was 81.6%. The mean basal cortisol value was 23.24 and the mean cortisol response was 6.22. The mean age (41.95 vs. 50.98), APACHE Score (16.63 vs. 16.44), pH (7.32 vs. 7.36) and sodium levels (135.55 vs. 134) were not significantly different between poor responders and good responders. **Conclusions:** (1) Relative adrenal insufficiency (hypocortisolemia) in vasopressor dependant critically ill patients is common (>80%). (2) In view of the high prevalence of hypocortisolemia in prolonged critical illness (as demonstrated by this study) and recent literature demonstrating benefit with replacement of glucocorticoids and mineralocorticoids in patients with relative adrenal insufficiency, it may be worthwhile considering steroid replacement in Indian patients in an ICU setting.

Key Words: Hypocortisolemia; Septic Shock; Adrenal insufficiency

Introduction

The neuroendocrine response to critical illness consists primarily of activated anterior pituitary function, and inactivation of peripheral anabolic pathways.¹ The HPA axis responds differently to acute and chronic insults.

Stimulation of the HPA axis, resulting in an elevated plasma level of cortisol, is one of the most important hormonal reactions to severe insults. Cortisol has a vital role in the maintenance of normal vascular tone and in potentiating the vasoconstrictor action of catecholamines. Glucocorticoids are both critical facilitators of adaptive response to stress and powerful immunosuppressive agents. Elevated levels of proinflammatory cytokines including TNF- α (Tumor Necrosis Factor- μ), IL1 (Interleukin-1) and IL6 (Interleukin-6) are found in plasma of patients with septic shock.^{2,3} The degree of cytokine elevation correlates with the degree of homeostatic disturbance and inversely correlates with survival.^{4,5} It

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seems probable that IL-6 plays a crucial role in the non-ACTH mediated activation of adrenal cortex during critical illness. On the other hand, glucocorticoids are able to inhibit IL-6 production by the immune cells.^{6,7} There is a prompt and sustained rise in both ACTH and cortisol in response to any form of stress. This is accompanied by a loss of circadian variability and ACTH pulsatility. Cortisol concentrations have been found to be elevated in most severe illnesses. Hence plasma cortisol levels seem to reflect severity of illness.⁸

Some of the recent studies have pointed out that adrenal insufficiency or hypocortisolemia are associated with a higher mortality. Concentrations regarded as normal in healthy individuals may be inadequate in critically ill patients—i.e., they may have a “Relative adrenocortical insufficiency”. Earlier literature quotes a wide range in the incidence of hypocortisolemia in the critically ill;⁹ this may be attributable to the different types of illnesses encountered from centre to centre. If the proportion of critically ill patients who end up in this state of ‘adrenal exhaustion’ is large, the result may help in outlining policies for the role of temporarily replacing the function of the normal adrenal gland by administration of physiological doses of glucocorticoids.

Through the SHIPS study, efforts were made to determine the prevalence of relative adrenocortical insufficiency to help in outlining the need for intervention, in caring for a critically ill vasopressor dependent patient in the Indian setting.

Aim

To estimate the prevalence of relative adrenocortical insufficiency in critically ill vasopressor dependent patients in a medical intensive care setting in India.

Objectives

1. To determine the prevalence of relative adrenocortical insufficiency in critically ill patients in a medical intensive care setting in India, with shock requiring vasopressors for more than 24 hrs, to maintain a mean arterial pressure of 70 mmHg.
2. To identify clinical risk factors (markers) of a poor cortisol response.

Methodology

Study design: Prospective, single arm analysis.

Duration of study: August 2001 to August 2002.

Inclusion Criteria

All patients in medical ICU requiring intensive care for more than 24 hours and fulfilling the following criteria were included in the study.

1. Systolic pressure less than 90 mm Hg despite adequate fluid replacement therapy
2. Requiring vasopressors for more than 24 hours, to maintain a minimum mean arterial pressure of 70 mmHg.

Exclusion Criteria

1. Patients with a known disease of the HPA axis (itself causing adrenal insufficiency).
2. Current consumption of drugs interfering with the cortisol assay like glucocorticoids and spironolactone.
3. Patients with a known HIV infection.
4. Patients above the age of 80 years.

Study Protocol

On enrolment into the study, a complete history and physical examination was performed. Clinical examination included an evaluation for a pre-existing HPA axis abnormality. Venous blood was drawn for the following tests: complete blood count, platelet count, prothrombin time, electrolytes, urea, creatinine and liver function tests. Arterial blood gas examination was performed. If a working diagnosis of sepsis was considered, blood, urine and suction tip cultures were dispatched for analysis.

All patients had a central venous catheter and a Foley's urinary catheter inserted for a close monitoring of central venous pressures and urine output. APACHE-II scoring was performed to assess the severity of illness.

Within 24 hours of enrolment to the study, a basal serum cortisol was taken. A bolus intravenous injection of one microgram of synthetic ACTH (Synacthen) was administered. (250 mcg of Synacthen was put into 500 ml of saline and 2 ml of this solution was used to get the strength of 1 mcg). Thirty and sixty minutes later, venous blood samples were drawn for Serum Cortisol analysis.

The samples thus collected were frozen and stored below minus 20° C in the biochemistry laboratory. These

samples were later thawed and the cortisol values were measured using solid phase radioimmunoassay (Coat-a-Count Cortisol assay from Diagnostics Products Corporation). The minimum detectable concentration by this kit was 0.2 mcg/dl. The intra assay coefficient variance of this method is < 5. Thus the cortisol values-basal, 30 min post ACTH, and 60 min post ACTH was measured using Radioimmunoassay.

The final outcome – alive and stable, alive but unstable, and dead - were also noted in all the study patients.

Sample size

From the existing data, the incidence of adrenal insufficiency in patients with septic shock varied from 20-75%,^{5,11,12} and in most studies, between 20 and 40%. However all the studies available were done on a western population. Keeping these limitations in mind, and assuming the prevalence to be lower, we decided to go by the study done from the New York Medical College in 95, which quoted a prevalence rate of 23%.⁵ Sample size was calculated using the formula: $4 pq/d^2$ where p denotes the prevalence, q = (100-p) and d, the expected difference between the two arms under study.

With a prevalence rate of 23% and a precision of 0.1, the sample size works out to be 71. But it works out to be 75, if the maximum quoted prevalence rate of 75% and a precision of 0.1 are to be used. Hence we decided to study a total of 75 patients. However, in the 1-year period we performed an interim analysis and terminated the study with 49 patients.

Results

We used the criteria of an increment in the cortisol response of 9 mcg/dl or less to diagnose relative adrenal insufficiency. By this, the prevalence of relative adrenal insufficiency in the study group was 81.6% (95% Confidence Intervals ranging from 70.75%- 92.45%). (Table: 1)

The study population was divided into those with a good cortisol response (CR > 9) and those without (CR < 9). We performed significance testing to identify predictors of poor cortisol response. Various parameters- age, mean arterial pressure, pH, serum sodium, APACHE-II score - were compared between the two groups and there was no significant difference between the groups. (Table 2) None were found to have any significant correlation with

Table 1: Distribution of cortisol response (CR) in the study population

CR Values	Frequency	Percent	Cumulative percent
-3	1	2.0	2.0
-1	6	12.2	14.3
0	2	4.1	18.4
1	2	4.1	22.4
2	5	10.2	32.7
3	3	6.1	38.8
4	8	16.3	55.1
5	2	4.1	59.2
6	7	14.3	73.5
7	2	4.1	77.6
9	2	4.1	81.6
10	1	2.0	83.7
11	1	2.0	85.7
12	2	4.1	89.8
14	1	2.0	91.8
16	1	2.0	93.9
25	1	2.0	95.9
36	1	2.0	98.0
41	1	2.0	100.0
Total	49	100.0	

This table demonstrates a prevalence of 81.6% for a cortisol response of 9mcg/dl. The standard error was 10.85 and the 95% Confidence Intervals ranged from 70.75%- 92.45%.

Table 2: Comparison of the two groups

	CR	N	Mean
Age	CR < 9	40	41.95
	CR > 9	9	50.78
MAP	CR < 9	40	100.83
	CR > 9	9	85.51
pH	CR < 9	39	7.32
	CR > 9	9	7.36
Na	CR < 9	40	135.55
	CR > 9	9	134.00
APACHE II	CR < 9	40	16.63
	CR > 9	9	16.44
Basal Cortisol	CR < 9	40	22.45
	CR > 9	9	26.78
30' Cortisol	Total	49	23.24
	CR < 9	39	25.05
60' Cortisol	CR > 9	9	47.00
	Total	48	29.11
Cortisol Response	CR < 9	31	23.90
	CR > 9	7	33.00
Cortisol Response	Total	38	25.58
	CR < 9	40	3.20
Cortisol Response	CR > 9	9	19.67
	Total	49	6.22

a poor cortisol response. There was no significant relation between mean arterial pressure and cortisol response (Table 3).

Recent studies have shown that poor cortisol response was associated with a poor outcome. Though our study was not designed in terms of numbers to assess mortality, we looked if any such trend was seen. In this study, though a majority of patients who died (76.0%) had a poor cortisol response, there was no significant correlation

Table 3: Mean arterial pressure Vs. cortisol response

MAP	CR<9	CR>9	Total
<70	14	1	15
>70	26	8	34
Total	40	9	49

Chi-Square Value = 1.974; P-value = 0.160

tion between mortality and poor cortisol response (Table 4).

Only 32.7% of patients were stable at discharge and 51% died in the hospital.

Gram-negative sepsis (most of them *Pseudomonas*, *Klebsiella* and *E. coli*) accounted for 76.09% of all these patients with sepsis. Suction tip culture was the most commonly identified source of sepsis. This could account for the high mortality compared to the overall mortality rate in our ICU, which is 30%.

Discussion

Absolute Adrenal insufficiency (AI) is considered to be present when the basal cortisol value is <100 nmol/L (4 mcg/dl).^{10,12} Relative adrenal insufficiency is defined as an inadequate response to exogenous ACTH, despite a normal or high basal cortisol level. Several authors have documented an inadequate incremental increase in plasma cortisol level after stimulation with 250 mcg of ACTH in subgroups of patients with septic shock. This indicates a reduced secretory reserve of cortisol, which may impair the individual's ability to cope with the sepsis, induced immune reactions and stress.

Previous meta-analyses of data¹³ show no definite benefit and even suggest a possible detrimental effect in using supraphysiological doses of steroids in patients with septic shock. However some subsequent studies have shown benefit with low dose steroid replacement in similar groups of patients. If hypocortisolemia (relative adrenal insufficiency) in patients with septic shock suggests a steroid deficient state, and if the occurrence of this problem reaches a significant magnitude in our patient population, there may be a beneficial role for ster-

Table 4: Outcome Vs. cortisol response

Outcome	CR<9	CR>9	Total
Alive and well	14	2	16
Alive but unstable	7	1	8
Dead	19	6	25
Total	40	9	49

Chi-square Value = 1.080; 2 sided Significance = 0.583

oids in septic shock.

Earlier studies suggest that the 1 mcg Synacthen test is more sensitive²⁰ to detect adrenal insufficiency, hence we preferred using the same to the conventional 250 mcg synacthen test. The main drawback of the 1 mcg test is that the peak response is unpredictable and would occur either at 30 minutes or at 60 minutes. Hence, the cortisol values at both 30 minutes and 60 minutes post synacthen were estimated and the higher of the two values used to estimate the cortisol response.

There are a variety of criteria for the normal values for this test: minimum peak levels of 18 mcg/dl,¹⁴ 19 mcg/dl,¹⁵ and 21 mcg/dl,¹⁶ and minimum increment of 7 mcg/dl¹⁷ and 9 mcg/dl,¹⁸ The incidence of relative AI in a recent well-conducted French study, using 250 mcg ACTH stimulation test and criterion of minimum increment of 9 mcg/dl, was 76.58%. We in this study considered the same criterion of minimum incremental increase of 9 mcg/dl, to make a diagnosis of relative adrenal insufficiency. Using this criterion, the prevalence of hypocortisolemia was 81.6% (95% CI: 70.75%- 92.45%). This is in keeping with the previous reported figure of 76.58% (95% CI: 71.79%-81.37%).¹⁹

The slightly higher prevalence of relative adrenal insufficiency noted in this study could be attributed to the following reasons. Firstly, we used 1mcg synacthen (LDSST) to identify patients with relative adrenal insufficiency. Low Dose Short Synacthen Test (LDSST) using 1 mcg synacthen has been shown to have a higher sensitivity than the conventional Short Synacthen Test (SST) using 250-mcg synacthen, in identifying patients with secondary adrenal insufficiency.

The mean basal value of cortisol in this study was 23.4 mcg/dl. In such a situation, using the criteria of a peak level of more than 18, 19 or 21 mcg/dl to exclude relative adrenal insufficiency would be inappropriate. Hence the criterion based on a minimal incremental increase of 9 mcg/dl would be more appropriate to assess the adequacy of adrenal response. A high mean basal cortisol value would mean that prior to the Synacthen stimulation itself, the adrenal is already in a stimulated state and its ability to respond to continued stress is limited. This suggests an exhaustion of the adrenal gland. The high prevalence of relative adrenal insufficiency in this

study, suggests that the vast majority of patients who are dependant on vasopressors are not capable of mounting a cortisol response adequate for the amount of stress. This is in keeping with the current concept of suppression of the HPA axis in prolonged critical illness.⁹ This raises the issue of replacement of physiological doses of corticosteroids in this group of nonresponders to Synacthen, to maintain the normal physiological response to stress and help them tide over the stressful event. In a recent randomized, double blind, placebo controlled, parallel group study, it has been demonstrated that treatment with low doses of hydrocortisone and fludrocortisone significantly reduced the risk of death in patients with septic shock and relative AI without increasing adverse events.¹⁹

We have performed tests of significance to identify predictors of poor cortisol response. None of the parameters including age, mean arterial pressure, blood pH, serum sodium and APACHE-II score had any significant correlation with poor cortisol response. Based on this, there was no parameter that could predict a poor cortisol response. Hence it may be necessary to do a Synacthen test in the entire group of vasopressor dependant critically ill patients, to identify those among them with relative adrenal insufficiency.

Thus, when financial constraints are present and laboratory facilities are not easily available, considering the high prevalence of relative hypocortisolemia, would it be cost-effective to identify and treat only those with relative adrenal insufficiency? In a French study,¹⁹ among the responders, there was no significant effect - beneficial or harmful - of corticosteroids on the 28th day in ICU, and on 1-year mortality rates. Hence it may be cost-effective to treat all vasopressor dependant critically ill patients with low dose corticosteroids. This issue needs further evaluation in a randomized controlled study.

We did not demonstrate a significant correlation between the final outcome and poor cortisol response. This is in contrast to previous studies, which demonstrated that a poor cortisol response is a poor prognostic indicator. This is because our study was not designed to look at mortality in terms of the sample size.

With a high incidence of septic shock and relative adrenal insufficiency, one needs to reconsider the role of

steroids. In view of the earlier studies using supraphysiological doses of steroids in patients with septic shock showing a harmful effect, and recent studies using lower doses (physiological doses) of steroid showing benefit in a subset of critically ill patients, who seem to be the majority, the minimum beneficial dose of steroids needs to be determined.

Conclusions

Relative adrenal insufficiency (hypocortisolemia) in vasopressor dependant critically ill patients is common. In this study we demonstrate a prevalence of 82%. In view of the high prevalence of hypocortisolemia in prolonged critical illness (as demonstrated by this study), and a recent study showing benefit with replacement of physiological doses of steroid in patients with relative adrenal insufficiency, it may be worthwhile considering steroid therapy in this subset of ICU patients.

No clinical or laboratory parameter predicted poor cortisol reserve and relative adrenal insufficiency.

Ideally, it would be suitable to do the synacthen stimulation test in critically ill vasopressor dependant patients, to identify those with relative adrenal insufficiency. When finances are limited and laboratory facilities are not always available, considering the high prevalence of relative hypocortisolemia, it may be a worthwhile and cost-effective approach to treat all these subjects with low dose steroids. However further randomized controlled trials are needed to identify the minimum required daily dosage and composition of steroid replacement in critically ill patients with relative adrenal insufficiency.

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