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Adrenal Insufficency in Patients With Low Systolic Blood Pressue and Features of SIRS or Sepsis

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ABSTRACT

Sepsis is one of the most common and prevalent conditions in the intensive care unit which is associated with high rate of morbidity and mortality. Sepsis is frequently associated with adrenal insufficiency, which may lead to hemodynamic instability. Critical illness-related corticosteroid insufficiency (CIRCI) is associated with a poor prognosis. Through this study efforts were made to determine the prevalence of relative adrenocortical insufficiency in critically patient with features of SIRS or sepsis. A cross sectional study was conducted among patients admitted to the medical intensive care unit to detect adrenal insufficiency using the 1mcg ACTH test (Synacthen test) in patients with low systolic blood pressure(≤ 90 mmof Hg) and features of sepsis or systemic inflammatory response syndrome (SIRS). High proportion of critically ill patients with systolic blood pressure ≤ 90 mm of Hg were noted to have relative adrenal insufficiency with 63.3% positive after Synacthen test. A statistically significant mean increment of 10.97mcg/dL was noted. The high percentage of relative adrenal insufficiency in this study suggests that vast majority of patients who are dependent on vasopressors are not capable of mounting a cortisol response adequate for the amount of stress.

KEYWORDS : Adrenal iInsufficiency, SIRS, Sepsis

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. An increase in tissue corticosteroid levels during acute illness is an important protective response. 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 pro inflammatory cytokines including TNF-α (Tumor Necrosis Factor- α), IL-1 (Interleukin-1) and IL-6 (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 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. Many diseases and their treatments interfere with the normal corticosteroid response to illness and thus induce tissue corticosteroid insufficiency. Subnormal cortisol production is the hallmark of the condition Chronic primary adrenal insufficiency, first recognized by Addison in 1844 and described in 1855. [9] Absolute adrenal insufficiency is considered to be present when the basal cortisol value is < 100 nmol/L (4 mcg/dl).[10,11] Concentrations regarded as normal in healthy individuals may be inadequate in critically ill patients i.e., they may have a "relative adrenocortical insufficiency". Relative adrenal insufficiency is defined as an inadequate response to exogenous ACTH, despite a normal or high basal cortisol level.

Earlier literature quotes a wide range in the incidence of hypocortisolemia in the critically ill;[12] this may be attributable to the different types of illnesses encountered. Critical illness-related corticosteroid insufficiency (CIRCI) is associated with a poor prognosis. Through this study efforts were made to determine the prevalence of relative adrenocortical insufficiency in critically patient with features of SIRS or sepsis. The deficiency of cortisol secretion by the adrenal cortex has been shown to increase morbidity and mortality in patients with septic shock.[13] The continued suppression of adrenocortical function increased the mortality rate in critically ill patients.[14]Septic shock has been associated with mortality rate greater than 50%.[15,16]

There are various methods for diagnosis of adrenal insufficiency in critically ill patients are baseline (random) cortisol concentration estimation, standard (250 mcg) and the low-dose (1 mcg) corticotropin stimulation tests. 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. The frequency and diagnosis of adrenal insufficiency in critically ill patients remain controversial. Adrenal insufficiency is estimated to occur at a rate of 0-30% in the critically ill[17,18] and may be as high as 25-40% in patients with septic shock,[19,20] depending on the specific tests and threshold used to diagnose adrenal insufficiency, underlying disease, and severity of illness.

Earlier studies by Abdu TAM et al suggest that the 1 mcg Synacthen test is more sensitive[21]to detect adrenal insufficiency, hence we preferred using the same to the conventional 250 mcg Synacthen test. There are a variety of criteria for the normal values for this test: minimum peak levels of 18 mcg/dl,[22]19 mcg/dl,[23]and 21 mcg/dl,[24]and minimum increment of 7 mcg/dl[20] and 9 mcg/dl.[19] 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.

Administration of corticosteroids to adrenalectomized animals improved survival.[25] No definite benefit has been shown in previous meta-analysis of data by Cronin L et al[26] and even suggest a possible detrimental effect in using supraphysiological doses of steroids in patients with septic shock. However some recent studies with lower doses (physiological) of steroid replacement have shown benefit in a subset of critically ill patients. If hypocortisolemia (relative adrenal insufficiency) in patients with septic shock suggests a steroid deficient state, and if the proportion of critically ill patients who end up in this state of adrenal exhaustion is large, there may be a beneficial role for steroids in septic shock. So it may be important to diagnose those patients who are dependent on vasopressors and are not capable of mounting an adequate cortisol response to stress.

OBJECTIVE: To detect adrenal insufficiency using 1mcg ACTH test (Synacthen Test) in patients with low systolic blood pressure(≤ 90 mm

of Hg)and features of sepsis or SIRS.

MATERIALS AND METHODS: A cross sectional study was done among patients admitted to the medical intensive care unit of a tertiary care teaching hospital. Patients with low systolic blood pressure (≤ 90mm of Hg) and with features of SIRS or sepsis were included. Patients were considered to have SIRS if they presented with any 2 of the following features: Fever (>38^{0}C) or hypothermia (< 36^{0}C); Tachypnea (>24 breaths/min); Tachycardia (heart rate >90/min); Leukocytosis (>12000/µl); Leucopenia (< 4000/µl). Patients on antihypertensive medications; patients on steroids; patients with history of coronary artery disease and those with HIV infection were excluded.

An 8.00 AM. basal serum cortisol was measured. 1mcg ACTH was given intravenously. ACTH was prepared by adding Synacthen (25mcg) to 25ml of 0.9% saline in glass bottle and 1 ml of the resulting solution containing 1mcg ACTH was used and unused solution was stored at 4^{0}C. Then serum cortisol was measured again after 1 hour. Post-ACTH serum cortisol values >18mcg/dL was taken as normal. Serum sodium, potassium & random blood sugar were also measured.

Various laboratory parameters of Synacthen test positive patients were compared with test negatives using t test or Chi-square test.

RESULTS AND DISCUSSION: In this study a total 30 patients with a systolic blood pressure ≤ 90 mm of Hg with features of SIRS or sepsis admitted in ICU were enrolled. The age of participants ranged from 20 – 76 years with a mean of 59.43 years (±12.741). Table 1 gives the baseline parameters of the participants. The mean basal serum cortisol value noted in this study was 9.24 mcg/dl.

TABLE 1: BASELINE MEASUREMENTS

	Minimum	Maximum	Mean	Std. Deviation
Pulse Rate	98	122	109.47	5.73
Temperature	98.8	102.0	100.293	0.84
SBP supine	84	90	87.73	1.72
DBP supine	60	74	68.53	4.87
SBP sitting	80	88	83.20	3.31
DBP sitting	60	72	65.00	4.86
Hemoglobin	8.7	16.2	11.263	1.95
Total leucocyte count	13140	28880	18239.67	3969.003
Platelet	16000	520000	183466.67	117455.12
Urea	22	132	57.37	34.53
Creatinine	0.5	5.6	2.293	1.41
Na+	130	145	138.37	4.41
K+	4	6	4.28	0.62
RBS	82	221	111.17	32.40
Baseline Serum Cortisol	6.4	12.6	9.24	1.84

Table 2 shows the mean serum cortisol level pre- and post-ACTH administration. The mean increment of 10.97mcg/dL noted was found to be statistically significant (t 9.5; p<0.001).

TABLE 2: PRE AND POST SERUM CORTISOL LEVEL

	Mean	SD	Minimum	Maximum	t value	Significance
Pre-ACTH serum cortisol	9.24	1.84	6.4	12.6	9.507	**<0.001**
Post-ACTH serum cortisol	20.21	7.65	11.3	36.8		

A cut off level of more than 18mcg/dL would be appropriate to exclude relative adrenal insufficiency and assess the adequacy of adrenal response. So using this cut off, out of the 30 patients, 19 (63.3%) were positive after Synacthen test (serum cortisol level <18 mcg/dL after 1mcg Synacthen test) and 11 (36.7%) were test negative (>18 mcg/dL). Also based on the criterion of an increment < 9mcg/dl taken as Synacthen test positive, 19 patients were positive (63.3%). Previous studies have shown the proportion varying from 22% to 75%. [16,17,18]

The mean age of Synacthen test negative patients was 64.91 years(±9.18) whereas that of the positive patients was 56.26 (±13.63) as shown in Figure 1 but this observed difference was not significant[t value 1.87; p 0.073]. Looking into the gender distribution (Table 3) of those with test positive and negative, it was also found to be statistically non-significant [Chi square 0.072; p 0.789].

FIGURE 1: Mean Age (Years) of Synacthen Test Positives and Negatives

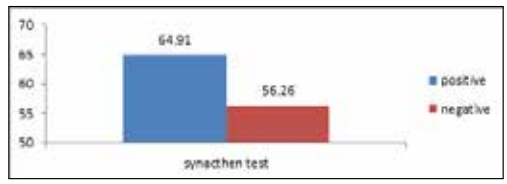

TABLE 3: Gender Distribution of Synacthen Test Positives and Negatives

Gender	Synacthen test		Total
	Positive	Negative	
Female	4	6	10
Male	7	13	20
Total	11	19	30

Table 4 depicts the values of various parameters pre and post ACTH administration. The postural drop in systolic blood pressure of 4.53 mm of Hg (t 8.366; p <0.001) and drop of 3.53 mm of Hg in diastolic blood pressure (t 4.983; p <0.001) from sitting to supine posture were found to be significant. There was no significant difference in supine systolic blood pressure of those with test positive and negative. But in sitting systolic blood pressure the mean in those with positive test was 81.58mmHg and those with negative test was 86 mmHg it was statistically significant. Similarly diastolic blood pressure both in supine and sitting was statistically significant between those with positive and negative test. Other vital parameters like pulse rate, temperature, etc.did not show any statistically significant difference between Synacthen positive and negative patients [Table 4].

TABLE 4: COMPARISON OF VITAL PARAMETERS

	Test inference	Minimum	Maximum	Mean	SD	t value	p value
Pulse Rate	Negative	98	118	108.55	5.592	0.66	0.512
	Positive	100	122	110.00	5.888		
Temperature	Negative	98.8	102.0	100.291	.9181	0.01	0.991
	Positive	99.0	102.0	100.295	.8093		
SBP supine	Negative	86	90	88.00	.894	0.64	0.528
	Positive	84	90	87.58	2.063		
DBP supine	Negative	70	74	71.82	1.662	3.24	0.003
	Positive	60	74	66.63	5.123		
SBP sitting	Negative	82	88	86.00	2.000	4.59	<0.001
	Positive	80	88	81.58	2.795		
DBP sitting	Negative	68	72	70.36	1.206	8.67	<0.001
	Positive	60	68	61.89	3.089		

Most of the laboratory parameters studied did not show any significant difference between Synacthen positive and negative patients [Table 5]. In this study, low sodium and high potassium showed a statistically significant (<0.001) difference between the Synacthen test positive and test negative patients. Similarly significant difference was noted in the serum cortisol both pre- ACTH and post-ACTH administration.

TABLE 5 : COMPARISON OF VARIOUS LABORATORY PARAMETERS

	Test inference	Minimum	Maximum	Mean	SD	t value	p value
Hemoglobin	Negative	8.7	15.5	12.03	1.94	1.68	0.104
	Positive	8.8	16.2	10.82	1.87		
Total Leukocyte Count	Negative	13140	28880	17620.9	4579.35	0.64	0.525
	Positive	14400	28880	18597.9	3655.15		

Platelet Count	Negative	45000	334000	220454.55	105131.69	1.33	0.194
	Positive	16000	520000	162052.63	121515.19		
Blood Urea	Negative	26	130	57.55	29.17	0.02	0.983
	Positive	22	132	57.26	38.05		
Serum Creatinine	Negative	0.9	4.4	1.85	1.02	1.34	0.190
	Positive	.5	5.6	2.55	1.56		
Serum Sodium	Negative	140	145	142.27	1.56	4.97	<0.001
	Positive	130	142	136.11	3.91		
Serum potassium	Negative	4	4	3.78	0.14	4.14	<0.001
	Positive	4	6	4.56	0.61		
Random Blood Sugar	Negative	88	124	109.45	13.09	0.22	0.830
	Positive	82	221	112.16	39.92		
Serum Cortisol pre-ACTH	Negative	9.6	12.6	10.96	1.08	5.48	<0.001
	Positive	6.4	11.2	8.25	1.41		
Serum cortisol post-ACTH	Negative	24.2	36.8	29.61	3.62	16.17	<0.001
	Positive	11.3	16.6	14.77	1.36		

Most of the Synacthen test positive patients (18 out of 19) when compared to 36.36% of the test negative patients (4 out of 11) were on vasopressors. This difference was found to be statistically significant [chi square 9.337; p 0.002].The high percentage of relative adrenal insufficiency in this study suggests that vast majority of patients who are dependent 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 HPA axis in prolonged illness.[12]

Sepsis with gram negative bacteria was the most common cause in those with adrenal insufficiency (Figure 2).

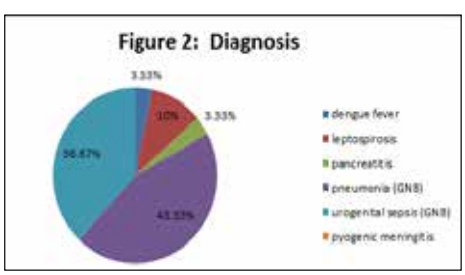

TABLE 6: RELATION BETWEEN DIAGNOSIS AND SYNACTHEN TEST

Diagnosis	Synacthen Test Inference		Total
	Negative	Positive	
Dengue	1	0	1
Leptospirosis	0	3	3
Pyogenic meningitis	0	1	1
Pancreatitis	1	0	1
Pneumonia (gram negative bacteria)	5	8	13
Urogenital sepsis (gram negative bacteria)	4	7	11
Total	11	19	30

The underlying cause for admission or sepsis was not related to the positivity or negativity of Synacthen test [Fischer's Exact NS p 0.424].

CONCLUSION: Relative adrenal insufficiency in critically ill patients with systolic blood pressure≤ 90 mm of Hg is common. In view of the high prevalence of hypocortisolemia in prolonged critical illness, it may be worthwhile considering steroid therapy in this subset of ICU patients. It may be necessary to do a Synacthen test in the entire group of critically ill patients, to identify those among them with relative adrenal insufficiency.

LIMITATIONS

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. But in our study only 1 hour value was measured.

Also mortality was not assessed in our study.

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