

GLUCOCORTICOID RESPONSE TO INTRAMUSCULAR ACTH STIMULATION IN CRITICALLY ILL PATIENTS

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ABSTRACT

BACKGROUND

Cortisol (Glucocorticoid) is the main hormone in host response to stress. Its secretion from adrenal glands depends on integrity of hypothalamic-pituitary-adrenal (HPA) axis. Adrenocorticotrophic hormone (ACTH) is the stimulant for cortisol secretion from adrenal glands. Adrenal insufficiency (AI) is often present in critically ill patients and is diagnosed by ACTH stimulation test using intravenous (IV) injection of Synacthen (Tetracosactide) which is not freely available in our part. Another synthetic corticotrophin (Acton Prolongatum) prepared by Ferring pharmaceuticals can be used for intramuscular (IM) ACTH stimulation test for assessment of adrenal function.

Aims & Objectives- To measure the basal serum cortisol level at 8.00-9.00 a.m. then at 60 min. & 3 hours after IM ACTH stimulation and to find out glucocorticoid response in critically ill patients.

MATERIALS AND METHODS

A descriptive study was designed in the Medical ICU of SCB Medical College, Cuttack, 46 critically ill adult patients with various diseases admitted to Medical ICU and were having or suspected of having some degree of adrenocortical dysfunction on the basis of prolonged hypotension for more than 6 hours despite adequate fluid challenge and/or need for vasopressors/inotropes, were included in this study for the period from Sep. 2013 to Sep. 2015.

RESULTS

Out of total 46 ill patients, 25 patients were diagnosed as adrenal insufficiency. Amongst them, 14 were male and 11 were female. Most of them presented with various combinations of hypotension, fever, nausea, vomiting, fatigue, pigmentation, weakness and irritability.

CONCLUSION

We concluded that intramuscular Acton Prolongatum can be used for ACTH stimulation test in critically ill patients to diagnose adrenal insufficiency (AI).

KEYWORDS

Critically Ill Patient, Intensive Care Unit (ICU), Adrenal Insufficiency, Acton Prolongatum, ACTH Stimulation Test.

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BACKGROUND

Severe illness and stress activate the hypothalamic-pituitary-adrenal (HPA) axis and stimulate the release of corticotrophin (adrenocorticotrophic hormone or ACTH) from the pituitary gland, which in turn increases the release of cortisol from adrenal cortex.^{1,2}

This activation is an essential component of the general adaptation to illness and stress and contributes to the maintenance of cellular and organ homeostasis. Adrenalectomised animals succumb rapidly to haemorrhagic and septic shock and steroid replacement is protective against these challenges.^{3,4} Even minor degrees of adrenal insufficiency increases the mortality in critically ill or injured patients.⁵ Our study aims to diagnose adrenal insufficiency in critically ill patients on the basis of ACTH stimulation test.

MATERIALS AND METHODS

After clearance from institutional ethics committee (IEC), we have designed a descriptive study in the Medical ICU of SCB Medical College, Cuttack, 46 critically ill adult patients with various diseases admitted to Medical ICU were included in the study from Sept. 2013 to Sept. 2015. The samples were taken conveniently. Informed consent was obtained from the patient's next of kin.

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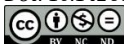
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Patient selection criteria: Critically ill patients of various diseases admitted to Medical ICU and were having or suspected of having some degree of adrenocortical dysfunction on the basis of prolonged hypotension for more than 6 hrs. despite adequate fluid challenge and/or need for vasopressors/inotropes, were included in the study.

Exclusion criteria: Patients were excluded if they had known previous conditions that may have disrupted the HPA axis.^{6,7,8,9}

In selected patients, detailed history and thorough clinical examination was done and disease activity score was recorded in a proforma. Basal cortisol was estimated between 8.00 a.m. to 9.00 a.m. (0 hr.), then they underwent ACTH stimulation test by intramuscular (IM) injection of 25 units of Acton Prolongatum (synthetic corticotropin carboxymethyl cellulose-available as 5 mL vial with concentration of 60 units/mL) and blood collected at 1 hr. for estimation of serum cortisol. Another blood sample at 3 hrs. was also collected in 20 patients for further analysis and correlation. We determined the absolute and proportional changes between the basal cortisol level and the peak response to ACTH (Delta cortisol at 1 hr = difference of values of serum cortisol between 1 hr. and 0 hr.). Cortisol was measured by Electrochemiluminescence immunoassay (ECLIA) used on Roche Cobas e 411 immunoassay analyser. The following investigations were done daily, complete blood count (CBC), plasma electrolytes, glucose levels, serum creatinine and liver function tests, arterial lactate and blood gases.

Hydrocortisone administration (starting at 100 mg intravenous, every 8 hours) was initiated while awaiting the ACTH test results. If the test was considered normal, hydrocortisone was discontinued.

Statistical Analysis

The observed data set was statistically analysed by using IBM-compatible Statistical Package for the Social Sciences (SPSS) version 20.0. The qualitative data were expressed as numbers (%), while the continuous quantitative data as mean ± standard deviation (SD) and the data was statistically analysed by using the following tests: Student t-test, Chi-square test. A p-value of <0.05 was considered significant and p-value of <0.001 was considered highly significant, while p-value of >0.05 was considered not significant.

RESULTS

Sl. No.	Sex	No. of Cases	Percentage (%)
1	Male	32	69.56%
2	Female	14	30.43%
3	M + F (Total)	46	100%

Table 1. Sex Distribution of Suspected Cases of AI

Out of 46 study population, 32 were male and 14 were female [Table 1].

Sl. No.	Sex	No. of Cases	Percentage (%)
1	Male	14	56%
2	Female	11	44%
3	Total	25	100%

Table 2. Sex Distribution of Relative Adrenal Insufficiency (RAI) Patients from Total Patients, n=25

Out of 46 patients, 25 (54.39%) patients have relative
Out of 20 cases, 5 patients had ≤ 500 nmol/L basal serum cortisol, and 13 patients had Delta cortisol at 1 hr. of ≤250 nmol/L and

adrenal insufficiency (RAI) and 21 (45.65%) patients show the normal response to ACTH stimulation test. Amongst the 25 RAI patients, 14 (56%) were male and 11 (44%) were female. [Table 2].

Sl. No.	Age (In years)	No. of Cases, n=25	(%)
1	15-30	3	12%
2	31-45	12	48%
3	46-60	7	28%
4	>60	3	12%

Table 3. Age Distribution among RAI Patients. n=25

Out of the total RAI cases, 12 (48%) cases were found in the age group of 31-45 years, 7 (28%) were between 46 to 60 years, 3 (12%) from 15-30 and rest 3 patients (12%) were above 60 years. [Table 3].

Symptoms	Patients No.	Percentage (%)
Weakness and Fatigue	22	88%
Nausea and Vomiting	18	72%
Fever	17	68%
Pigmentation	6	19.98%
Diarrhoea	3	9.99%
Hypotension	25	100%
Irritability	9	29.97%
Depression	4	13.32%

Table 4. Clinical Presentation of Cases of Adrenal Insufficiency (n=25)

All of the cases taken were hypotensive (100%). 22 patients (88%) of them presented with generalised weakness, 18 patients (72%) presented with nausea and vomiting, 17 (68%) with fever, 9 (29.7%) patients were irritable and 4 patients (13.32%) were depressive at the time of presentation.

Sl. No.	Sex	Basal S. Cortisol ≤500 nmol/L	Increment Of S. Cortisol ≤250 nmol/L (Delta Cortisol at 1 hr.)
1	Male	9	14
2	Female	8	11
3	Total	17 (36.95%)	25 (54.34%)
4	Mean ± SD	202.62 ± 125.60	137.51 ± 68.18

Table 5. Result of ACTH Stimulation Test from 46 Critically ill Patients

Out of total 46 critically ill patients, 17 (36.95%) patients had ≤500 nmol/L basal S. cortisol (at 0 hr.) and after ACTH stimulation test, 25 (54.34%) patients had relative adrenal deficiency at 1 hr. S. cortisol level. [Table 5].

Sl. No.	Sex	S. Cortisol (Basal) ≤500 nmol/L	Delta 1 hr. ≤250 nmol/L	Delta 3 hrs. ≤250 nmol/L
1	Male	1	6	4
2	Female	4	7	4
3	Total	5 (25%)	13 (65%)	8 (40%)
4	Mean ± SD	200.73 ± 138.67	150.67 ± 64.42	174.03 ± 74.86

Table 6. Result of ACTH Stimulation Test of 20 Patients and Level of S. Cortisol at 0 hr., 1 hr., 3 hrs.

8 (40%) patients had Delta cortisol at 3 hrs. of ≤ 250 nmol/L. [Table 6].

Sl. No.		Adrenal Insufficiency	Normal Adrenal Function	P value
1	Cases	25	21	
2	Age (Years)	46.76 \pm 14.03	51.08 \pm 12.49	
3	Sex (Male: Female)	14:11	18:3	
4	Basal Cortisol (nmol/L)	137.51 \pm 68.18	529.52 \pm 261.63	<0.0001
5	Post ACTH Cortisol (nmol/L)	605.92 \pm 389.67	919.85 \pm 288.53	<0.0001
6	Range	30.48-1650	332-1576	
7	Delta Cortisol at 1 hr. (nmol/L)	135.51 \pm 68.25	349.28 \pm 154.42	<0.0001
8	Range	0.83-250	264-775	

Table 7. Cortisol Levels in Study Group, n=46

There was statistically significant difference in Basal cortisol, Post ACTH cortisol and Delta Cortisol between patients having AI and normal adrenal function.

DISCUSSION

The integrity of HPA axis is a major determinant of the host's response to stress.^{6,7} During stress, the activation of HPA axis is highlighted by increased corticotrophin release from the pituitary gland,¹⁰ enhanced adrenal secretory activity,^{11,12} and high plasma cortisol levels. However, whether endogenous glucocorticoid levels are adequate or constitute an independent predictor of death remains controversial.^{1,13,14} There are some studies which reported lower cortisol levels in non-survivors compared with survivors.^{15,16,17} For this reason, in stress, the evaluation of appropriateness of the activation of the HPA axis requires dynamic testing. Adrenal insufficiency is diagnosed when on stimulation test the peak serum cortisol is <500 nmol/L (18 $\mu\text{g/dL}$),¹⁸ alternatively it has been proposed that increment during ACTH stimulation test <250 nmol/L (9 $\mu\text{g/dL}$) or basal cortisol <83 nmol/L (3 $\mu\text{g/dL}$) can be considered as diagnostic of AI.^{18,19}

Diagnostic evaluation of suspected cases of adrenal insufficiency is hindered by non-availability of injection Synacthen. To overcome this limitation, we used Acton Prolongatum (Corticotrophin Carboxymethyl cellulose) as intramuscular ACTH stimulation test. During standard Synacthen stimulation test (SST), serum cortisol is taken at 30 min. and 60 min. intervals, because the serum cortisol (reflecting serum ACTH level) following injection of Synacthen peaks around this time. But the use of long acting corticotrophin carboxymethyl cellulose (Acton Prolongatum), plasma level of plasma 11- hydroxycorticosteroid reflecting the level of serum cortisol peaks around 1 to 3 hrs. (at 1 hr. 25.7 $\mu\text{g}/100$ mL and at 3 hrs. 37.4 $\mu\text{g}/100$ mL).²⁰ So we decided to take samples of serum cortisol at 0 hr., 1 hr. and 3 hrs. All the patients of control groups achieved normal stimulation of cortisol after intramuscular ACTH.

Intramuscular ACTH test with Acton Prolongatum is economically cheaper as compared to Synacthen. Synacthen costs around Rs. 3200 in the grey market. Each vial of Acton Prolongatum costs Rs. 1645 and contains 300 units (5 mL vial, 60 units/mL), thus 12 tests can be performed at a cost of Rs 130 each.

The incidence of adrenal insufficiency in critically ill patients presenting with shock varies and depends on the underlying disease and severity of illness. The reported incidence varies widely depending on the population of the patients studied and diagnostic criteria used to diagnose adrenal insufficiency.

Adrenal insufficiency: Subjects with post ACTH cortisol

<500 nmol/L (18 $\mu\text{g/dL}$) and Incremental response is decreased if serum cortisol rise was <250 nmol/L (9 $\mu\text{g/dL}$) from basal cortisol level post ACTH.²¹

Abhay Gundgurthi et al²² has done a study-“Intramuscular ACTH Stimulation Test for Assessment of Adrenal Function” and reported sex distribution among AI patients M: F =28:9 and age distribution mean \pm SD =33.0 \pm 18.8 yrs. Present study shows the sex distribution among AI patients M: F =14:11 and mostly affected age group 31-45 years (48%) with mean \pm SD is 46.76 \pm 14.03 years. [Table-1] and [Table-3].

Hypotension refractory to fluids and requiring vasopressors is the most common feature of acute adrenal insufficiency.²³ In the present study, 100% patients (25 patients) have hypotension and 88% (22 patients) had weakness and fatigue and 72% (18 patients) had symptoms of nausea and vomiting. Out of 25 patients, 17 patients (68%) presented with fever. CNS dysfunction as irritability and depression is common, frequently as a result of underlying disease. In the present study, 29.97% (9 patients) presented with irritability and 13.33% (4 patients) presented with depression as clinical features. [Table-4].

Acute adrenal insufficiency occurs in patients who are unable to increase their production of cortisol during acute stress. This includes patients with hypothalamic and pituitary disorders (Secondary AI) and patients with destructive diseases of adrenal glands (primary AI). Most common cause of acute adrenal insufficiency is sepsis and the SIRS.^{23,24} Abhay Gundgurthi et al²³ reported a mean basal cortisol 95.97 \pm 83.32 nmol/L, post ACTH cortisol 270.32 \pm 140.25 nmol/L and Delta cortisol 174.62 \pm 113.57 nmol/L, in 37 adrenal insufficiency patients out of 89 studied patients. The present study shows mean basal cortisol of 137.51 \pm 68.18 nmol/L, post ACTH cortisol 605.92 \pm 389.67 nmol/L and Delta cortisol 135.51 \pm 68.25 nmol/L in 25 adrenal insufficiency patients out of 46 studied patients. [Table-7]. Basal cortisol level solely cannot be relied on to detect all cases of AI.²³ From studied group, 17 patients had basal cortisol ≤ 500 nmol/L. and 25 patients had increment of S. cortisol ≤ 250 nmol/L. Out of 17 patients whose basal cortisol was <500 nmol/L, 5 patients had >250 nmol/L of S. cortisol after ACTH stimulation test.

14 patients from 25 patients had increment of S. cortisol ≤ 250 nmol/L, but they did not have basal cortisol ≤ 500 nmol/L. Only 9 patients had both basal cortisol ≤ 500 nmol/L and increment value of S. cortisol after ACTH ≤ 250 nmol/L. Two patients from control group had subnormal basal cortisol but showed increment >250 nmol/L S. cortisol after ACTH stimulation test. Hence, at best, basal cortisol can be used to screen for suspected AI and those with a low basal cortisol will need a stimulation test to confirm or exclude AI.

CONCLUSION

Adrenal insufficiency is often present in critically ill patients,²⁵ but difficult to prove due to non-availability of Synacthen stimulation test. In this study, we have shown that AI can be easily and efficiently diagnosed using Acton Prolongatum, which is an easily available long acting version of ACTH.

HPA dysfunction is common in severely ill patients. Even slight impairment of the adrenal response to severe illness can increase morbidity and mortality, and we believe that low serum cortisol levels may be the cause rather than the consequence of poor outcome in these patients. Therefore, a high index of suspicion for adrenal insufficiency is required in all critically ill patients, particularly those with refractory hypotension. All patients with suspected HPA dysfunction should be treated with stress doses of corticosteroids. The result of our study points to the possibility of existence of subnormal adrenocortical response in some critically ill patients, who do not respond adequately to the standard optimal therapy. Therapeutic implication arising out of the study is the possible role of glucocorticoids as an adjunctive therapy, in the hope of a more favourable outcome.

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