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Prospective evaluation of admission cortisol in trauma

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ABSTRACT

Background A low cortisol level has been shown to occur soon after trauma, and is associated with increased mortality. The purpose of this study was to investigate the impact of low cortisol levels in acute critically ill trauma patients. We hypothesized that patients would require increase vasopressor use, have a greater blood product administration, and increased mortality rate.

Methods A blinded, prospective observational study was performed at an American College of Surgeons verified Level I trauma center. Adult patients who met trauma activation criteria, received initial treatment at Community Regional Medical Center and were admitted to the intensive care unit were included. Total serum cortisol levels were measured from the initial blood draw in the emergency department. Patients were categorized according to cortisol ≤15 μg/dL (severe low cortisol, SLC), 15.01–25 μg/dL (relative low cortisol, RLC), or >25 μg/dL (normal cortisol, NC) and compared on demographics, injury severity score, initial vital signs, blood product usage, vasopressor requirements, and mortality.

Results Cortisol levels were ordered for 280 patients; 91 were excluded and 189 were included. Penetrating trauma accounted for 19% of injuries and blunt trauma for 81%. 22 patients (12%) had SLC, 83 (44%) had RLC, and 84 (44%) had NC. This study found patients with admission SLC had higher rates of vasopressor requirements, required more units of blood, and had a higher mortality rate than both the RLC and NC groups.

Conclusion Low cortisol level can be identified acutely after severe trauma. Trauma patients with SLC had larger blood product requirements, vasopressor use, and increase mortality. Initial cortisol levels are useful in identifying these high-risk patients.

Level of evidence Prognostic/epidemiologic study, level III

INTRODUCTION

The role of the hypothalamic–pituitary–adrenal (HPA) axis and adrenal insufficiency (AI) in critically ill patients has been extensively studied over the last 20 years.[1–4] The physiological response to stress involves the activation of the HPA axis leading to secretion of adrenocorticotrophic hormone (ACTH). This stimulates the adrenal cortex to secrete cortisol.[5] Cortisol has several important functions in the stress response including increasing blood glucose concentrations, reducing the number and function of immune cells, and augmenting blood pressure by increasing sensitivity of the vascular smooth muscle to vasopressor agents.[6–8] Activation of the HPA axis during stress or critical illness typically results in plasma cortisol levels greater than 25–30 μg/dL.[9]

Critical illness-related corticosteroid insufficiency (CIRCI) refers to the dysfunction of the HPA axis during critical illness either through decreased responsiveness to ACTH or decreased production of cortisol.[1 10] The rate of CIRCI is reported to range from 10% to 20% in medical intensive care unit (ICU) patients and up to 60% in patients with septic shock.[1 11] Several studies have examined CIRCI in the trauma population admitted to the ICU. The prevalence of CIRCI in trauma has been reported to range from 50% to 80%.[10 12–14] However, the definition of AI has not been uniform. Stein *et al* used a single admission cortisol level in patients with hemorrhagic shock to describe "AI." This study concluded that AI can occur immediately after acute injury from hemorrhagic shock, but did not address other severe trauma mechanisms.[15]

We hypothesize that low serum cortisol levels can be identified acutely after severe trauma, regardless of mechanism, and are associated with increased resuscitation requirements and worse outcomes.

METHODS

A blinded, prospective, observational cohort study was performed at Community Regional Medical Center (CRMC), a 650 bed, American College of Surgeons verified Level I trauma center in Fresno, California from January 2015 to May 2016. Patients 18 years and older who met trauma activation criteria, received initial treatment at CRMC, and subsequently admitted to the ICU, were included. The institution's trauma activation criteria include any hypotensive episodes (systolic blood pressure (SBP) <90 mm Hg) including the pre-hospital phase, Glasgow Coma Scale (GCS)<10 with mechanism related to trauma, patients intubated in the pre-hospital setting, gunshot wound (GSW) to head, neck, chest, abdomen, or extremities proximal to the elbow or knee, impaled objects to the head, neck, or torso, traumatic amputation proximal to the wrist or ankle, paralysis, and crushed, degloved, or mangled extremity.

Patient information was obtained from the trauma registry and chart review. This included demographic data, mechanism of injury (MOI), injury severity score (ISS), abbreviated injury score (AIS), vital signs on admission, base deficit, admission serum albumin level, blood products including packed red blood cells, fresh frozen plasma, platelets, and cryoprecipitate given in the first 24 hours, any pressor requirements for hypotension within
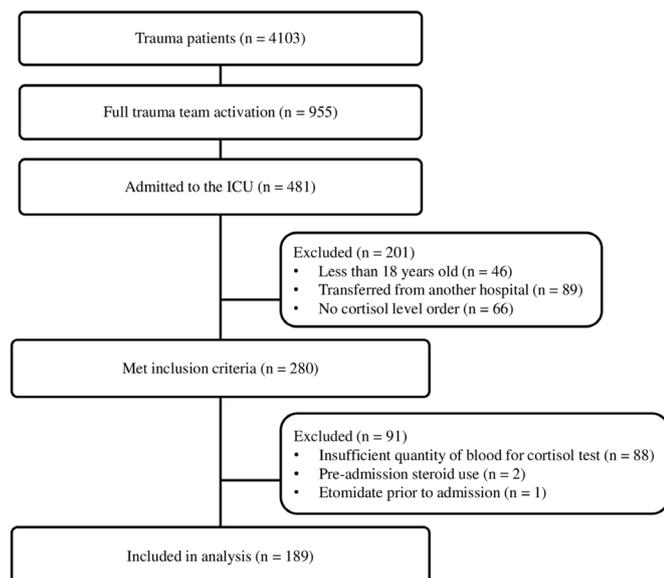
Figure 1 Inclusion/exclusion of patients. ICU, intensive care unit.

72 hours of admission, cosyntropin stimulation test results, ventilator days, and hospital and ICU lengths of stay (LOS).

Blood was collected on admission as part of the trauma activation protocol and total serum cortisol levels were obtained from this sample using the Beckman Coulter UniCel DXI Immunoassay chemistry analyzer. Blood samples were stored up to 72 hours; eligible patients were identified by the study coordinator and a study-specific order was submitted to the hospital laboratory. If sufficient blood remained after initial trauma protocol testing, the serum cortisol test was performed and test results returned to the study coordinator. These cortisol levels were not entered into the patient's electronic medical records, and were not available to the treating physician. Patients were excluded if an insufficient quantity of blood remained or blood was discarded prior to the cortisol order. Patients were also excluded if they had documented previous steroid use or received etomidate for endotracheal intubation.[16]

Cortisol level was categorized as "severe low cortisol" (SLC) for patients with an initial total serum cortisol level less than or equal to 15 µg/dL, "relative low cortisol" (RLC) for cortisol levels ranging from 15.01 to 25 µg/dL, or "normal cortisol" (NC) with cortisol levels greater than 25 µg/dL.[17] Groups were compared by demographics, MOI, admission serum albumin levels, initial vital signs, ISS, AIS, cosyntropin stimulation test, if performed, ventilator days, and hospital and ICU LOS. Primary outcomes included blood products administered within the first 24 hours of admission, continuous vasopressor requirements in the ICU within the first 72 hours of admission, and mortality. Patients receiving vasopressors for spinal or cerebral perfusion were not counted as requiring vasopressors.

Sample size calculations were based on Stein et al,[15] which reported 80% mortality in patients with SLC and 41% in patients with RLC. This study also demonstrated unequal numbers of patients in these groups with a 5:1 ratio of patients with RLC to SLC. Using these data, a similar difference in mortality could be detected at 80% power (α=0.05) with 16 patients in the SLC group and 78 patients in the RLC and NC groups.

All treating surgeons were blinded to the initial cortisol level. Evaluation for CIRCI was done at the discretion of the treating surgeon and consisted of a high dose ACTH test with a 250 µg cosyntropin stimulation test with cortisol levels drawn prior to

cosyntropin administration and at 30 and 60 min after administration. The cosyntropin stimulation test was ordered and was generally performed on patients who were consistently hypotensive and requiring vasopressors (for hemodynamic stability) despite adequate resuscitation. Patients with a change of less than 9 µg/dL were considered to have AI and were started on 200–300 mg hydrocortisone daily for 7 days as steroid replacement.

Continuous data are presented as mean±SE of the mean or median (IQR) and categorical data are presented as percentages. Groups were compared with χ^2 tests for categorical data and Mann–Whitney U or Kruskal–Wallis tests for continuous data. Multivariate regressions were performed to control for confounding variables. For these regressions, patients were categorized as either "NC" or "low cortisol," which combined both the RLC and SLC groups. Statistical analyses were performed using the Statistical Package for Social Sciences (IBM SPSS Statistics for Windows, V.23.0. Armonk, NY: IBM Corp.) and significance was attributed to a p value less than 0.05. This study was approved by Institutional Review Board for Community Medical Center and University of California, San Francisco, Fresno.

RESULTS

During the study period, 4103 trauma patients were entered into the trauma registry, of which, 955 had trauma team activations. Of these, 481 patients were admitted to the ICU. A total of 201 patients were excluded, 46 were less than 18 years old, 89 were transferred from another hospital, and 66 did not have orders for cortisol levels, leaving 280 patients that met inclusion criteria. Of these patients, 88 were ineligible due to an insufficient quantity of blood or blood discarded prior to order, two were excluded for pre admission steroid use, and one was excluded for receiving etomidate prior to admission, yielding a cohort of 189 patients (figure 1). The 88 patients that did not have a cortisol level obtained were compared with the 189 patients in the study group and did not differ in age, GCS, vital signs, ISS, AIS, or MOI.

The majority of patients (146/189, 77%) were men and average age was 42±1 years. Penetrating trauma accounted for 19% of injuries and blunt trauma accounted for 81% of injuries with a majority occurring as a result of motor vehicle or motorcycle collision. Median ISS was 22 (17–29) with overall mortality of 14% (26/189). Patients had trauma activations for GCS<10 (n=92), SBP <90 mm Hg (n=53), mechanism (GSW to the head, chest, abdomen, or proximal extremities) (n=22), cardiopulmonary resuscitation in progress (n=10), intubated in the pre-hospital setting (n=6), spinal cord injury with paralysis (n=5), and traumatic amputation (n=1).

Time to blood serum collection was 8 (5–13) minutes from time of patient's arrival. Total cortisol level ranged from 3.77 to 86.85 µg/dL with an average level of 24.60 µg/dL. The majority of patients in the study group had some degree of decreased cortisol level (105/189, 56%). Of the 189 patients in the study group, 22 (12%) had SLC, 83 (44%) had RLC, and 84 (44%) had NC.

Figure 2 depicts the distribution of cortisol level according to trauma activation criteria. In patients that arrived in traumatic arrest, 4 of 10 (40%) had SLC after injury. These patients represent 18% (4/22) of the SLC group. RLC was found in 63% (14/22) of patients with GSW to head, chest, abdomen or proximal extremities and 53% (28/53) with hypotensive episodes.

Comparing the SLC group to the RLC and NC group, there was no significant difference in age, GCS, heart rate, base deficit
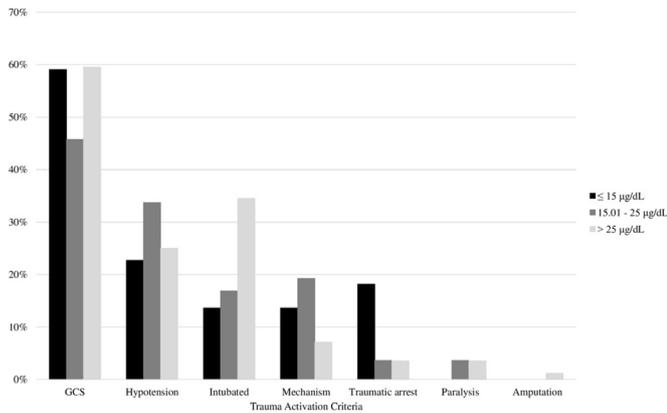
Figure 2 Trauma activation criteria by cortisol level on hospital arrival. GCS, Glasgow Coma Scale

or head AIS between the three groups. The group with NC had higher admission SBP and lower ISS, chest AIS, and abdomen/pelvis AIS than those with SLC (table 1).

The amount of blood products given within 24 hours of admission was significantly higher in patients with SLC when compared with the other groups (p<0.001). A total of 53 patients required vasopressors within the first 72 hours of admission. Of those, 33 patients, who required vasopressors for spinal or cerebral pressure perfusion, were excluded, leaving a total of 19 patients on vasopressors for cardiovascular instability. Patients in the SLC

group had increased vasopressors requirements within 72 hours of admission than those in the other groups (p=0.001).

There were a total of 26 deaths; 17 from severe brain injury, 7 from multisystem organ failures, and two from spinal cord injuries. The mortality rate was higher in patients with SLC when compared with the RLC and NC groups. The groups did not differ in hospital or ICU LOS, or days on the ventilator (table 2). Using multivariate regression, low cortisol, ISS, and age were associated with mortality, and low cortisol and ISS were associated with increased vasopressor requirements (table 3).

There were 12 patients included in this study with adrenal injuries, two of which were bilateral. Of these, five had SLC, five had RLC, and two had NC. Two of the patients died, both of which were in the SLC group. Vasopressors were used in four of these patients, two SLC and two RLC.

Of the 189 patients in our study, 19 (10%) had a cosyntropin stimulation test ordered by the treating surgeon, who were blinded to the initial cortisol value. There was a greater percentage of cosyntropin stimulation tests ordered in the group with SLC (5/22, 23%) than in the RLC (7/83, 8%) and NC groups (7/84, 8%). Eight patients had a change in cortisol less than 9 µg/dL. Of these eight patients, four were in the SLC group, three in the RLC group, and one in the NC group. All were started on steroid replacement therapy. In all, 74% (14/19) of cosyntropin stimulation tests were done within 72 hours of the patients' arrival.

DISCUSSION

This study found patients with admission SLC had higher rates of vasopressor requirements, required more units of blood, and had a higher mortality rate than both the RLC and NC groups. When controlling for confounding variables, both ISS and low admission cortisol were associated with increased vasopressor requirements. Age, ISS, and low admission cortisol were associated with increased mortality.

The occurrence of AI in critically ill trauma patients has been described.[12–15 18 19] However, most of these studies have used a single low cortisol value as the definition of AI and the cortisol value used as the threshold for AI also varied by study. Two studies examined AI over the course of the patients' ICU stay. In a study of 22 ICU patients, Offner et al found an AI incidence of 60% within the first 10 days of ICU admission using a total cortisol level of less than 18 µg/dL as the definition for AI.[12] A 2006 study of 44 trauma patients admitted to the ICU showed a prevalence of relative AI of 41%, defining AI as cortisol level less than 25 µg/dL.[13] Stein et al showed similar results in a study of 60 patients in hemorrhagic shock, where a single admission cortisol level of less than 14.5 µg/dL best predicted 24 hours mortality.[15]

Few studies have examined low cortisol levels in the acute trauma setting. One study looked at total cortisol levels in trauma patients within 2 hours of injury and found a correlation with ISS. In severely injured patients (ISS greater than 13), cortisol levels were lower than in the less injured patients.[18] A more recent study found a strong association between low cortisol and increased mortality in patients with acute hemorrhagic shock. SLC (cortisol less than 10 µg/dL) was present in 17% of the patients.[15] Our study of 189 patients is the largest study to date evaluating cortisol levels on admission in the critically ill trauma patient. Over half of the severely injured patients (ISS 22 (17–29)) were found to have lower than NC (56%) on arrival to the emergency department (ED.

AI has been associated with high mortality in patients with septic shock.[1 2 4 5] The use of total serum cortisol level as a

Table 1 Clinical characteristics on admission by cortisol level

| | Severe low cortisol | Relative low cortisol | Normal cortisol | |
	≤15 µg/dL	15.01–25 µg/dL	>25 µg/dL	P value
N	22 (12%)	83 (44%)	84 (44%)	–
Male gender	16 (73%)	67 (81%)	63 (75%)	0.59
Mechanism of injury				
Bike/Ped v auto	4 (18%)	12 (15%)	8 (10%)	0.45
Fall	1 (4%)	4 (5%)	18 (21%)	0.002
MVC/MCC	12 (55%)	41 (49%)	32 (38%)	0.22
Other blunt	2 (9%)	5 (6%)	15 (18%)	0.054
GSW/SW	3 (14%)	21 (25%)	11 (13%)	0.11
Age	44±3	40±2	44±2	0.44
GCS	6 (3–12)	12 (3–15)	8 (3–15)	0.18
SBP	97 (78–115)	110 (80–116)	126 (94–144)*	0.027
HR	104 (69–122)	92 (80–116)	112 (90–125)	0.02
Base deficit	−5.2(−9.7 to −3.1]	−4.3(−7.4 to −2.8]	−4.6(−7.5 to −1.3]	0.46
Albumin	2.8 [2.4–2.9]	2.7 [2.5–3.1]	3.0 [2.7–3.4]*	0.01
ISS	29 (22–36)	26 (19–33)	22 (13 - 26)*	<0.001
AIS≥3				
Head/neck	13 (59%)	43 (52%)	52 (62%)	0.41
Chest	14 (64%)	49 (59%)	33 (39%)*	0.017
Abdomen/pelvis	10 (46%)	22 (27%)	11 (13%)*	0.003
Extremities	5 (23%)	23 (28%)	11 (13%)	0.064

*p < 0.05 compared with cortisol ≤15 µg/dL.
AIS, abbreviated injury scale; GCS, Glasgow Coma Scale; GSW, gunshot wound; HR, heart rate; ISS, injury severity score; MCC, motorcycle collision; MVC, motor vehicle collision; Ped, pedestrian; SBP, systolic blood pressure; SW, stab wound.

Table 2 Outcomes by cortisol level

	Severe low cortisol ≤15 µg/dL	Relative low cortisol 15.01–25 µg/dL	Normal cortisol >25 µg/dL	P value
N	22	83	84	–
Cortisol level	12.6 [8.5–14.2]	19.7 [18.1–21.8]*	29.8 [27.7–35.4]*	<0.001
Units of blood product within 24 hours	7 (1–25)	2 [0–6]*	0 [0–3]*	<0.001
Vasopressors within 72 hours‡	6 (38%)	10 (15%)*	3 (4%)*	0.001
High dose	5 (83%)	9 (90%)	2 (67%)	
Low dose	1 (17%)	1 (10%)	1 (33%)	
Cosyntropin stimulation test performed	5 (23%)	7 (8%)	7 (8%)	0.11
Ventilator days	10 (4–17)	6 (2–12)	7 (2–15)	0.16
ICU LOS (survivors)	15 (8–19)	7 (3–14)*	8 (4–17)	0.17
Hospital LOS (survivors)	26 (13–34)	17 (9–25)	19 (9–27)	0.14
Mortality	8 (36%)	12 (15%)*	6 (7%)*	0.002

Low dose=norepinephrine ≤ 5 mcg/min or phenylephrine ≤100 mcg/min; high dose=norepinephrine > 5 mcg/min or phenylephrine >100 mcg/min.
*p < 0.05 compared with cortisol ≤15 µg/dL.
‡Patients receiving vasopressors for spinal or cerebral perfusion were excluded from the total number of patients for percentage calculations.
ICU, intensive care unit; LOS, length of stay

prognostic indicator of outcomes and mortality continues to be debated in the trauma literature. Several studies have shown an association between mortality and AI in the trauma population.[15][20] In the present study, a statistically significant increase in mortality was found with lower serum cortisol levels. Mortality doubled from the NC group (7%) to the RLC group (15%) and increased fivefold in the SLC group (36%) (p=0.002)

The literature strongly supports treating septic patients with AI requiring vasopressors with steroid replacement. Septic patients that were treated had a significant reduction in pressor requirements with more rapid resolution of shock.[1][6][17] The treatment of AI in critically ill trauma patients has not been as extensively studied. One retrospective study with AI (defined as cortisol level less than 20 µg/dL or a change less than 9 µg/dL with a cosyntropin stimulation test) found a significant decrease in mortality (31% vs 19%) in those treated with hydrocortisone versus those not treated.[17] In this prospective, blinded study, the admission cortisol levels were not available to the treating clinicians. The practice of our 12 trauma critical surgeons is to order cosyntropin stimulation tests on patients that are persistently hypotensive on vasopressors despite adequate resuscitation. A greater number of patients in the SLC group versus RLC and NC

had a cosyntropin stimulation tests ordered and CIRCI treated. However, the sample size was too small to draw any conclusions regarding outcomes or mortality following treatment.

The inherent limitations to any observational trial include bias and the inability to draw conclusions about specific treatments. In an attempt to mitigate bias, the treating physicians were blinded to the initial cortisol levels. There were few patients who underwent cosyntropin stimulation tests and received steroid replacement therapy; therefore, this study was not powered to examine the effects of steroid treatments on patients with AI. Because outcomes are dependent on many factors, unknown confounding variables may have also contributed to the outcomes in the low cortisol groups. Another limitation of the present study is that 88 patients of 280 were excluded for insufficient blood samples. However, when comparing our cohort of 189 patients to the excluded patients, we found no difference in demographics, vital signs, or trauma data points; therefore, we believe that the patients who had levels drawn were representative of the population as a whole.

A single cortisol level drawn in the ED immediately after arrival identifies patients at risk for greater resuscitative requirements (blood products and pressors) and mortality in the trauma population. Trauma patients with SLC (cortisol level less than 15 mg/dL) had larger blood product requirements within 24 hours, increased vasopressor use within 72 hours, and increased mortality. This is the largest prospective observational study to date to evaluate the presence of cortisol in the trauma population in the resuscitative phase of care.

Table 3 Multivariate regression analysis of predictors of vasopressor requirements and mortality

	OR	95% CI	P value
Vasopressor requirements			
Low cortisol	3.9	1.01 to 14.9	0.048
ISS	0.95	0.91 to 0.99	0.012
Age	0.98	0.95 to 1.02	0.32
SBP	1	0.99 to 1.02	0.63
HR	1	0.98 to 1.02	0.80
Mortality			
Low cortisol	4.3	1.28 to 14.2	0.018
ISS	0.9	0.90 to 0.97	0.001
Age	0.9	0.90 to 0.96	<0.001
SBP	1	0.99 to 1.02	0.46
HR	1	0.97 to 1.01	0.31

ISS, injury severity score; SBP, systolic blood pressure; HR, heart rate.

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