Hyperacute adrenal insufficiency after hemorrhagic shock exists and is associated with poor outcomes

Deborah M. Stein, MD, MPH, Elliot M. Jessie, MD, MBA, Sean Crane, MD, Joseph A. Kufera, MA, Tracy Timmons, MD, Carlos J. Rodriguez, DO, MBA, Jay Menaker, MD, *and* **Thomas M. Scalea, MD,** *Baltimore, Maryland*

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From the R Adams Cowley Shock Trauma Center (D.M.S., E.M.J., T.T., C.J.R., J.M., T.M.S.), University of Maryland School of Medicine, Baltimore, Maryland; and Shock Trauma and Anesthesiology Research–Organized Research Center (D.M.S., S.C., J.A.K., J.M., T.M.S.), University of Maryland School of Medicine, Baltimore, Maryland.
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Address for reprints: Deborah M. Stein, MD, MPH, University of Maryland School of Medicine, Chief of Critical Care, Program in Trauma/Division of Critical Care, R Adams Cowley Shock Trauma Center, Baltimore, MD; email: dstein@umm.edu.

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BACKGROUND: Adrenal insufficiency (AI) has been extensively described in sepsis but not in acute hemorrhage. We sought to determine the incidence of hyperacute AI (HAI) immediately after hemorrhage and its association with mortality.

METHODS: Patients with acute traumatic hemorrhagic shock presenting to the R Adams Cowley Shock Trauma Center prospectively had serum cortisol levels collected on admission. Inclusion criteria were hypotension and active hemorrhage. Clinicians were blinded to results, and no patient received steroids in the acute phase. The primary outcome measure was death from hemorrhage within 24 hours of admission.

RESULTS: Fifty-nine patients were enrolled during an 8-month period. Mean admission cortisol level was 18.3 ± 8.9 μg/dL. Acute mortality rate from hemorrhage was 27%. Overall mortality rate was 37%. Severe HAI (serum cortisol level <10 μg/dL) was present in 10 patients (17%). Relative HAI (<25 μg/dL) was present in 51 patients (86%). Those who died of acute hemorrhage had significantly lower mean cortisol levels (11.4 ± 6.2 μg/dL vs. 20.9 ± 8.4 μg/dL, $p < 0.001$) as did patients who ultimately died in the hospital (12.8 ± 7.6 μg/dL vs. 21.6 ± 8.1μg/dL, $p < 0.001$). In multivariate analysis, cortisol levels were associated with mortality from acute hemorrhage, with an odds ratio of 1.17 (95% confidence interval, 1.02–1.35). Adjusted receiver operating characteristic analysis indicated that serum cortisol has a 91% accuracy in differentiating survivors of acute hemorrhage from nonsurvivors.

CONCLUSION: This study is the first to report that AI occurs immediately after acute injury during hemorrhagic shock and is strongly associated with mortality. HAI may be a marker of depth of shock but is potentially rapidly modifiable as opposed to other markers, such as lactate or base deficit. Further work is needed to determine whether steroid administration can change outcome in selected patients. (*J Trauma Acute Care Surg*. 2013;74: 363–370. Copyright © 2013 by Lippincott Williams & Wilkins)

LEVEL OF EVIDENCE: Prognostic/epidemiologic study, level III.

KEY WORDS: Hemorrhage; adrenal insufficiency; cortisol; mortality.

Despite advances in management of patients with hemorrhagic shock during the past several years, acute hemorrhage continues to be a leading cause of morbidity and mortality following trauma. Strategies such as damage control operative techniques and damage control resuscitation have decreased mortality rates,[1–4] but in both civilian and military trauma, hemorrhage accounts for approximately 30% to 40% of deaths following injury and is the most common cause of potentially preventable death.[5,6] It is well recognized that some patients, despite adequate surgical or angiographic hemostasis, will go on to die acutely because of the sequelae of profound hemorrhagic shock. The cause of this physiologic exhaustion following hemorrhage is multifactorial. The role of coaguloapthy, immune modulation, inflammation, and cellular and tissue hypoperfusion in cardiovascular collapse and death following hemorrhage is the subject of extensive investigation.[7–12] What has been less well studied, however, is the role of endocrine dysfunction in this process.

In the setting of sepsis, the importance of an intact hypothalamic-pituitary-adrenal (HPA) axis has been extensively described. During the past 20 years, adrenal insufficiency (AI) has been increasingly recognized as a significant contributor to death in the setting of septic shock.[13–15] The mechanism of AI and its contribution to cardiovascular collapse in the setting of sepsis are thought to be related to the role of cortisol on essential metabolic, vasoreactive, and immune system functions.[13] Several large randomized trials have demonstrated efficacy of treatment of patients with sepsis and septic shock with steroids.[13] Patients with AI treated with steroid replacement have a decrease in pressor requirements and greater reversal of shock.[13,16] The consequences of hemorrhagic shock are known causes of AI in critically ill and injured patients. There have been several studies that have investigated the role of AI after trauma in patients admitted to the intensive care unit (ICU),[7–21] a few of which have focused on patients with hemorrhagic shock.[22–25] No study, however, has specifically investigated the role of AI in the acute active phase of hemorrhage.

This study was designed to answer the question: Does hyperacute AI (HAI) exist in patients with acute hemorrhagic shock? In addition, we sought to determine whether low cortisol levels in the actively hemorrhaging phase of injury are associated with outcome.

PATIENTS AND METHODS

Consecutive patients who met inclusion criteria with acute traumatic hemorrhagic shock presenting to the R Adams Cowley Shock Trauma Center prospectively had serum collected on admission as part of their admission blood draws. Blood was sent for total serum cortisol analysis. Inclusion criteria were:

1. direct from scene of injury
2. hypotension as defined by (any one):
   a. any systolic blood pressure (SBP) less than 90 mm Hg within the first 10 minutes following admission
   b. two SBP readings less than 100 mm Hg within the first 10 minutes following admission
3. active hemorrhage defined by (any one):
   a. positive FAST (Focused Assessment with Sonography for Trauma)
   b. plan to go directly to the operating room
   c. uncrossmatched blood hung within the first 10 minutes from admission
   d. obvious external bleeding

All research activities and data collection were approved by the University of Maryland School of Medicine Institutional Review Board with a waiver of consent. All patients were managed according to the treating physician's clinical judgment. No cortisol values were made available to the clinical team, and no patient was given steroids in the acute phase of injury.

Total serum cortisol levels were run on the VITROS 5600 Integrated System (Ortho Clinical Diagnostics, New York). Total serum cortisol values of less than 10 μg/dL were considered diagnostic of severe HAI,[13,15] and values of less than 25 μg/dL

TABLE 1. Characteristics of Study Subjects

	All (N = 59)	Survived >24 h (n = 43)	Died of Acute Hemorrhage (n = 16)	*p*	Survived to Hospital Discharged (n = 37)	In-Hospital Deaths (n = 22)	*p*
Age, mean ± SD, yr	34.8 ± 15.6	35.3 ± 16.3	33.5 ± 14.0	0.7	36.0 ± 16.0	32.7 ± 15.0	0.4
Males, n (%)	51 (86.4)	36 (83.7)	15 (93.7)	0.3	31 (83.8)	20 (90.9)	0.4
Blunt mechanism, n (%)	30 (50.8)	23 (53.5)	7 (43.8)	0.5	18 (48.6)	12 (54.5)	0.7
Mechanism of injury, n (%)							
Gunshot wound	18 (30.5)	10 (23.3)	8 (50.0)	0.4	9 (24.3)	9 (40.9)	0.4
Motor vehicle crash	16 (27.1)	13 (30.2)	3 (18.8)		10 (27.0)	6 (27.3)	
Stabbing	11 (18.6)	10 (23.3)	1 (6.3)		10 (27.0)	1 (4.5)	
Pedestrian struck	6 (10.2)	4 (9.3)	2 (12.5)		3 (8.1)	3 (13.6)	
Motorcycle crash	5 (8.5)	4 (9.3)	1 (6.3)		3 (8.1)	2 (9.1)	
Fall	3 (5.1)	2 (4.6)	1 (6.3)		2 (5.4)	1 (4.5)	
ISS, mean ± SD	28.7 ± 15.0	25.8 ± 14.6	36.6 ± 13.4	0.01	23.2 ± 13.5	37.9 ± 12.8	<0.001
Predicted survival (TRISS), mean ± SD	0.61 ± 0.39	0.74 ± 0.32	0.27 ± 0.38	<0.001	0.81 ± 0.26	0.28 ± 0.34	<0.001
Admission SBP, mean ± SD, mm Hg	88.6 ± 57.4	106.3 ± 46.9	41.0 ± 57.3	<0.001	110.9 ± 43.4	51.3 ± 59.7	<0.001
Admission SBP ≤90, n (%)	29 (49.1)	16 (37.2)	13 (81.3)	0.004	12 (32.4)	17 (77.3)	0.001
No recordable BP on arrival, n (%)	13 (22.0)	3 (7.0)	10 (62.5)	<0.001	2 (5.4)	11 (50.0)	<0.001
Admission HR, mean ± SD, beats/min	91.9 ± 55.5	109.2 ± 40.2	45.5 ± 64.9	0.001	106.1 ± 40.5	69.8 ± 69.8	0.01
Admission HR ≥120, n (%)	21 (35.6)	18 (41.9)	3 (18.8)	0.1	14 (37.8)	7 (31.8)	0.6
Cardiac arrest, n (%)	11 (18.6)	1 (2.3)	10 (62.5)	<0.001	1 (2.7)	10 (45.4)	<0.001
ABC score, mean ± SD, median (IQR)	1.5 ± 0.8, 2 (1–2)	1.5 ± 0.9, 1 (1–2)	1.7 ± 0.6, 2 (1–2)	0.4	1.5 ± 0.9, 1 (1–2)	1.6 ± 0.7, 2 (1–2)	0.5
0, n (%)	6 (10.2)	6 (13.9)	0 (0.0)	0.2	5 (13.5)	1 (4.5)	0.4
1–2, n (%)	46 (78.0)	31 (72.1)	15 (93.8)		27 (73.0)	19 (86.4)	
3–4, n (%)	7 (11.9)	6 (13.9)	1 (6.3)		5 (13.5)	2 (9.1)	

Data were complete for all patients except one for whom ISS and TRISS were unavailable.
ABC, Assessment of Blood Consumption; HR, heart rate; TRISS, Trauma Score–Injury Severity Score.

TABLE 2. Initial Management

	All (n = 59)	Survived >24 h (n = 43)	Died of Acute Hemorrhage (n = 16)	*p*	Survived to Hospital Discharge (n = 37)	In-Hospital Deaths (n = 22)	*p*
Etomidate administration, n (%)	8 (13.6)	7 (16.3)	1 (6.3)	0.3	6 (16.2)	2 (9.1)	0.4
Blood product use, first 6 h							
PRBCs, median (IQR), U	7 (2–22)	7 (2–14)	7 (1–32)	0.1	4 (2–13)	21 (2–35)	<0.001
FFP, median (IQR), U	8 (0–18)	8 (2–13)	6 (2–22.8)	0.3	6 (0.5–11)	17 (0.3–28.8)	0.004
Platelets, median (IQR), U	0 (0–2)	0 (0–2)	0 (0–2)	0.8	0 (0–1)	1 (0–2)	0.09
Blood product use, first 24 h							
PRBCs, median (IQR), U	7 (2–22.5)	7 (2–14.5)	7 (1–32)	0.3	7 (2–13)	21 (2–36.5)	0.004
FFP, median (IQR), U	8 (0.5–20.5)	8 (2–15)	6 (2–22.8)	0.4	6 (2–12)	18 (0.3–28.8)	0.01
Platelets, median (IQR), U	0 (0–2)	0 (0–2)	0 (0–2.3)	0.7	0 (0–1.3)	2 (0–3)	0.2
Massive transfusion, n (%)*	26 (44.1)	19 (44.2)	7 (43.8)	1.0	13 (35.1)	13 (59.1)	0.08
Operative intervention on admission, n (%)	41 (69.5)	28 (65.1)	13 (81.3)	0.2	24 (64.9)	17 (77.3)	0.7
Hemostasis achieved, n (%)	52 (88.1)	43 (100.0)	9 (56.3)	<0.001	37 (100.0)	15 (68.2)	<0.001

*Defines as 10 or more units of PRBCs over 24 hours.
FFP, fresh frozen plasma; IQR, interquartile range; PRBC, packed red blood cells.

TABLE 3. Admission Laboratory Values

	All (n = 59)	Survived >24 h (n = 43)	Died of Acute Hemorrhage (n = 16)	*p*	Survived to Hospital Discharge (n = 37)	In-Hospital Deaths (n = 22)	*p*
Time from injury to blood draw, mean (SD), min	56.6 (26.3)	60.7 (26.1)	48.1 (25.4)	0.1	60.6 (27.9)	51.4 (23.7)	0.2
Cortisol, mean (SD), μg/dL	18.3 (8.9)	20.9 (8.4)	11.4 (6.2)	<0.001	21.6 (8.1)	12.8 (7.6)	<0.001
HCO_3, mean (SD), mmol/L	19.5 (4.6)	20.2 (4.3)	17.6 (5.2)	0.06	20.2 (3.9)	18.3 (5.5)	0.1
Lactate, mean (SD), mmol/L	9.2 (4.6)	8.0 (4.5)	12.4 (3.4)	<0.001	7.6 (4.5)	11.7 (3.8)	<0.001
Prothrombin time, mean (SD), s	17.3 (9.5)	15.8 (3.2)	21.5 (17.3)	0.04	15.3 (2.2)	20.8 (14.9)	0.03
INR, mean (SD)	1.6 (1.4)	1.4 (3.2)	2.2 (2.6)	0.06	1.3 (0.2)	2.1 (2.3)	0.04
Hematocrit, mean (SD), %	34.0 (6.2)	34.2 (6.2)	33.6 (6.5)	0.7	34.5 (6.1)	33.2 (6.5)	0.1
Platelet, mean (SD), $\times 10^6$/L	196.8 (78.5)	206.6 (82.8)	170.7 (60.1)	0.1	212.1 (83.9)	171.3 (62.0)	0.05

INR, international normalized ratio.

were considered relative HAI.[19,22] The primary outcome measure was death from acute hemorrhage within 24 hours of admission. Overall mortality was analyzed as a secondary outcome measure.

Univariate analysis of patient demographic, injury, and hospital characteristics as potential confounders was conducted between survivors and nonsurvivors. Means based on normally distributed continuous data were analyzed using Student's *t*-test, and Mann-Whitney U test was used to compare non-normally distributed continuous data. Categoric values were compared with Pearson's χ^2 statistic and Fisher's exact test. The adjusted effect of serum cortisol on mortality was ascertained in a multivariable logistic regression model by including variables that had a value of $p < 0.10$ in the univariate analysis and computing the Hosmer-Lemeshow goodness-of-fit statistic. A value of $p = 0.10$ would effectively remove unnecessary variables, yet allow for final analysis of 5 to 10 characteristics that would be small enough to yield true results for a sample size of 59 patients, would account for a variety of important diagnostic measures, and may result in statistically significant associations with outcome at the $p = 0.05$ level following adjustment. All potential independent variables that met the $p < 0.10$ inclusion criteria and were highly correlated were removed before final regression analysis to avoid issues with multicollinearity. In addition, some covariates were dichotomized because of their non-normality. Because of the small sample size, it was decided to analyze subgroups of patients with "hemostasis achieved" or "cardiac arrest" and not include those variables in the initial regression model. The odds ratio (OR) and its corresponding 95% confidence interval (CI) were computed for each factor in the regression models. Receiver operating characteristic (ROC) curves were plotted to summarize the sensitivity and specificity levels of serum cortisol and determine its classification accuracy with regard to outcome.

TABLE 4. Sensitivity and Specificity Analysis for Classification of Mortality (n = 59)

Cortisol, μg/dL	Mortality From Acute Hemorrhage		In-Hospital Mortality	
	Sensitivity, %	Specificity, %	Sensitivity, %	Specificity, %
<10	44	93	36	95
<15	75	81	64	84
<20	94	51	86	54
<25	100	19	95	19

RESULTS

Sixty patients were enrolled during an 8-month period. One patient was found to be on chronic steroids and was subsequently excluded from further analysis, leaving 59 patients that formed the patient population for this study. Baseline demographics of the entire study population are shown in Table 1. Figure 1 shows the major sources of hemorrhage for the study cohort. Twenty-four patients (40.7%) had multiple sources of bleeding. No patient was noted to have adrenal injury. Only 12 patients (20.3%) had a significant traumatic brain injury (TBI), defined as a Head Abbreviated Injury Scale score greater than 2.

Table 2 demonstrates the initial management of patients, and Table 3 demonstrates the mean admission laboratory values for the study population. Blood was drawn a mean of 56.6 ± 26.3 minutes from injury in the 46 patients (78.0%) for whom injury time was available. Ten patients (16.9%) had severe HAI (total serum cortisol level <10 μg/dL), and 51 patients (86.4%) had relative HAI (total serum cortisol level <25 μg/dL). Because much of the total cortisol measured in standard assays is protein bound, we also examined the degree of hypoalbuminemia in study patients. No correlation was noted between total serum cortisol and albumin levels drawn on admission as part of

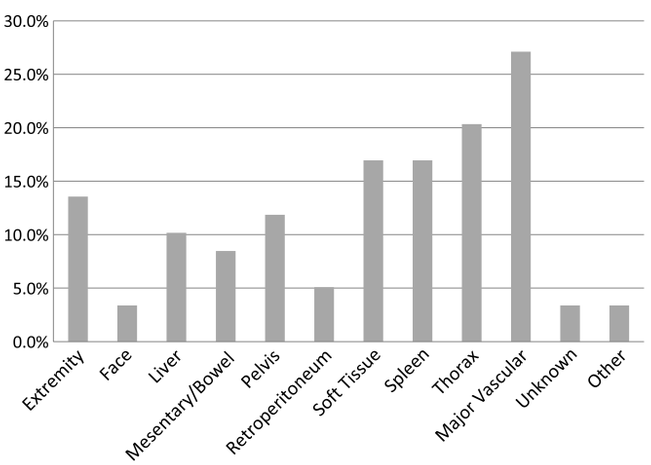

Figure 1. Sources of hemorrhage in study patients.

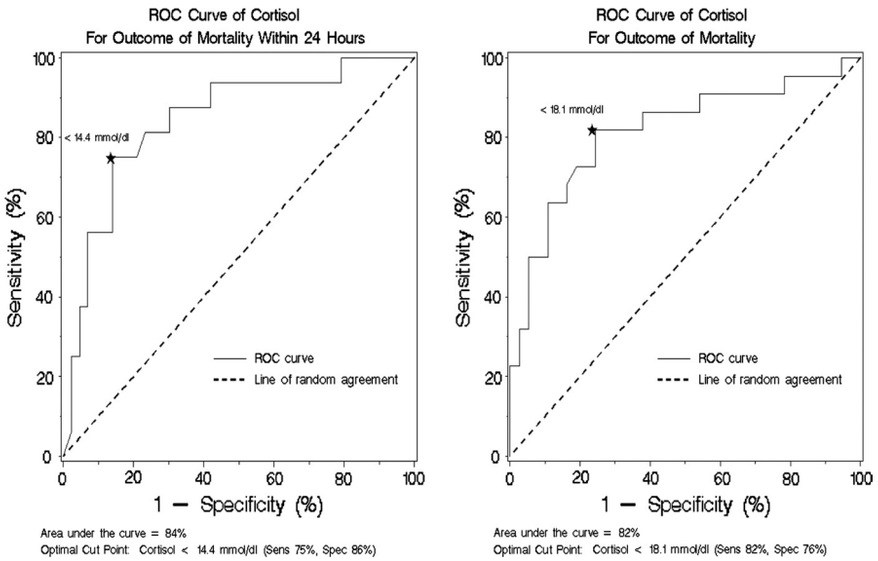

Figure 2. ROC curves of cortisol for acute and in-hospital mortality.

standard of care testing. In addition, because of associations of age, etomidate use, time of day, and TBI with serum cortisol levels reported in the literature, we also examined these effects and found no associations between these variables and cortisol levels (data not shown).

The mortality rate from acute hemorrhage (<24 hours after admission) was 27.1% (16 patients) at a median of 132 minutes (interquartile range [IQR], 33.2–279.2 minutes) from admission. An additional six patients died (three of sepsis and three of TBI) in the hospital on median hospital day 5 (range, 2–31 days) for an overall mortality rate of 37.3%. Overall median length of stay was 7.0 days (IQR, 0–18.8 days), and median ICU length of stay was 1.8 days (IQR, 1–12.2 days).

Tables 1 to 3 show the demographic, injury-specific data, initial management, and laboratory values stratified by death from acute hemorrhage and overall mortality. The mean serum cortisol level for the entire group was 18.3 μg/dL (95% CI, 16.0–20.6 μg/dL). Of the 10 patients with total serum cortisol levels of less than 10 μg/dL, the acute mortality rate from hemorrhage was 70.0% (7 patients) whereas overall hospital mortality rate was 80.0% (eight patients). Of the 51 patients with serum cortisol levels of less than 25 μg/dL, 16 (31.4%) died initially, whereas 21 (41.2%) did not survive to hospital discharge. In the eight patients with total serum cortisol levels of more than 25 μg/dL, all survived acutely and one died of sepsis on hospital day 31. Sensitivities and specificities for classification of acute and in-hospital mortality are shown in Table 4. Overall, in unadjusted analysis, the OR for cortisol level predicting acute mortality from hemorrhage was 1.23 (95% CI, 1.09–1.38; $p = 0.001$; $R^2 = 0.27$), indicating a 23% increase in mortality within 24 hours for a 1-μg/dL decrease in serum cortisol level. For prediction of in-hospital mortality, the OR was 1.20 (95% CI, 1.08–1.33; $p = 0.001$; $R^2 = 0.26$).

In multivariate analysis, when controlling for other patient and injury characteristics (SBP ≤90 mm Hg, Injury Severity Score [ISS] ≥25, lactate, international normalized ratio, platelet count), the OR for cortisol level predicting acute mortality from hemorrhage was 1.17 (95% CI, 1.02–1.35; $p = 0.02$; $R^2 = 0.38$) and overall hospital mortality was predicted by cortisol values with an OR of 1.15 (95% CI, 1.02–1.32; $p = 0.03$; $R^2 = 0.47$). The Hosmer-Lemeshow statistic indicated that the model fits the data well.

ROC analysis indicated that serum cortisol has an AUC of 84% (95% CI, 73–96%) for accuracy in predicting acute mortality from hemorrhage. The optimal threshold for maximum sensitivity and specificity is a serum cortisol level less than 14.4 μg/dL. Serum cortisol has an AUC of 82% (95% CI, 69–94%) for accuracy in predicting overall mortality, with an optimal threshold of less than 18.1 μg/dL (Fig. 2). In adjusted analysis, total serum cortisol level has 91% accuracy in differentiating survivors of acute hemorrhage from nonsurvivors.

A subgroup analysis was performed excluding the patients who presented in cardiac arrest or developed cardiac arrest shortly after admission group to evaluate the incidence of AI and the effect on mortality without the subset at exceptionally high risk of death. Mean total serum cortisol level in these 11 patients was 8.8 ± 4.5 μg/dL. Ten (90.9%) of these patients died of acute hemorrhage. When evaluating the rest of the study cohort, mean cortisol level in the 42 acute survivors was 21.1 μg/dL ± 8.4 μg/dL versus 16.3 μg/dL ± 5.5 μg/dL in the six who died of acute hemorrhage. Although cortisol levels tended to be slightly lower among those who died, this failed to reach statistical significance ($p = 0.1$). This result was confirmed in a multivariable model. When comparing hospital survivors to the 12 in-hospital deaths, total serum cortisol was higher in the 36 survivors, but this also failed to reach statistical significance (21.9 ± 8.0 μg/dL vs. 16.6 ± 7.8 μg/dL, $p = 0.06$). After excluding cardiac arrest patients, one patient (16.7%) in the acute hemorrhage death group had a serum cortisol level of less than 10 μg/dL and 100% had a serum cortisol level of less than 25 μg/dL. Of the in-hospital deaths, two patients (16.7%) had a serum cortisol level of less than 10 μg/dL and 11 patients (91.7%) had a serum cortisol level of less than 25 μg/dL.

An additional subgroup analysis was performed in which seven patients in whom surgical hemostasis was never achieved

were excluded. All of these patients obviously died acutely. The mean serum cortisol level in this group was 10.7 μg/dL ± 7.9 μg/dL. Of the nine patients in whom hemostasis was achieved but died of acute hemorrhage, the mean serum cortisol level was 11.8 μg/dL ± 8.8 μg/dL versus 20.9 μg/dL ± 8.4 μg/dL ($p = 0.003$) in the 43 patients who survived acutely. Mean cortisol level in the 37 hospital survivors was 21.6 μg/dL ± 8.1 μg/dL versus 13.8 μg/dL ± 7.6 μg/dL ($p = 0.002$).

DISCUSSION

Following injury, hemorrhage accounts for the largest proportion of deaths occurring within the first 24 hours.[5,6,26,27] Few deaths from hemorrhage occur after 24 hours,[6,27] but the sequelae of hemorrhagic shock are associated with increased rates of organ failure and sepsis.[28] Management of patients in the acute phase of hemorrhage obviously focuses on control of bleeding and replacement of blood volume.[4,10] Current models of hemorrhage control focus increasingly on early prevention or reversal of the "lethal triad" with damage control hemostasis and resuscitation techniques.[1–4,10] What has been less well studied in recent years is the role of the HPA axis in acute hemorrhage and resuscitation. This study attempted to address that by asking a very simple question: Does AI occur acutely in patients with active hemorrhagic shock? We believe that, based on our results, it does.

The HPA axis has numerous vital functions.[13] Cortisol increases catecholamines and angiotensin,[29] maintains microvascular perfusion through nitric oxide–mediated mechanisms,[30] and has significant anti-inflammatory actions,[31] as well as other roles. Given the known importance of these physiologic processes in hemorrhagic shock, it would stand to reason that dysfunction of the HPA axis in acute hemorrhage may contribute to worsening of these processes, lack of responsiveness to therapy, and possibly poor outcome. In the setting of sepsis, this phenomenon has been well described. AI may be caused by either adrenal or hypothalamic dysfunction or cortisol resistance.[13,18] AI has been shown to occur in 30% of patients with sepsis and 50% to 60% with septic shock.[14,15] Most of these patients have "reversible dysfunction"[32] that is either self-limited or can be addressed with steroid administration. In response to a major stressor, such as hemorrhage, the HPA axis should respond by increasing levels of adrenal stimulation and circulating catecholamines.[10,17,20,33,34] Total serum cortisol level should be greater than 25 μg/dL in a highly stressed patient.[34] There are several definitions of AI that can be used. An absolute total serum cortisol level of less than 9 μg/dL,[35] less than 10 μg/dL,[13,15] or less than 15 μg/dL[36] to define AI have been described. Alternatively, lack of increase in serum cortisol of at least 9 μg/dL in response to a cosyntropin stimulation test (CST) has been widely used for diagnosis.[13,23–25,35,36] Also described is the phenomenon of "relative" or "occult" AI at levels of less than 25 μg/dL.[19,22] For the purposes of this study, we used a total serum cortisol level of less than 10 μg/dL as our definition of severe AI. Severe AI was found to occur in 17% of patients in this study. In more than 85%, relative AI (serum cortisol level <25 μg/dL) was found. We recognize the limitations of a single total cortisol level being "diagnostic" of AI as a single random low level,[19] but clearly, a CST is not practical for early diagnosis of AI in an acutely hemorrhaging patient, and we wanted to use the most widely accepted and available measure to maximize generalizability of this study.

The concept of AI as a sequelae of hemorrhagic shock is not new. Numerous studies have evaluated the effect of hemorrhagic shock on the development of AI in critically ill and injured patients admitted to the ICU.[17–25] AI clearly exists after injury.[24] In two studies of patients admitted to the ICU with a diagnosis of hemorrhagic shock, relative AI was found in 93% and 62.5%.[22,23] Another study described the prevalence of occult AI in trauma ICU patients to be 51% to 81%.[19] This study is the first to show that AI, at least as defined by serum cortisol levels, occurs in the acute phase of injury at the time of active hemorrhage.

There are a few studies that have looked at cortisol levels early after injury. In a study of the effect of etomidate on adrenal suppression, baseline cortisol levels in trauma patients were found to be 31 μg/dL and 27 μg/dL in patients with a mean ISS of 26.5 and 20, respectively.[36] In another study, levels drawn less than 2 hours from injury ranged from 28 μg/dL to 34 μg/dL and were found to correlate with injury severity.[21] Neither of these studies specifically looked at patients in hemorrhagic shock and, in our more selected cohort, the cortisol levels were lower than previously reported, with a mean value of only 18 μg/dL.

We have also shown a significant association between AI and mortality, both in the first 24 hours from hemorrhage and overall mortality. Serum cortisol level was found to be 84% accurate in predicting acute mortality from hemorrhage, with levels less than 14.4 μg/dL having the highest combination of accuracy for correctly identifying deaths because of acute hemorrhage. Similarly, serum cortisol was 82% accurate in predicting overall mortality, with 18.1 μg/dL as the optimal threshold for correctly identifying death. The association between low cortisol levels and mortality held even when controlled for injury severity, admission physiology, and other admission laboratory values known to be markers of depth of shock. In adjusted analysis, we have demonstrated a 17% increase in risk of death from acute hemorrhage for every 1 μg/dL decrease in serum cortisol.

The real question raised by our data is whether severe or relative HAI is a contributor to morbidity and mortality and a potentially treatable consequence of hemorrhage or simply a marker of depth of shock and physiologic exhaustion. In one study of mixed nonseptic medical and surgical patients, the authors concluded that low cortisol levels were simply a marker of severity of disease.[17] In an effort to elucidate whether HAI contributes to death from acute hemorrhage or is simply a consequence of unrecoverable shock, we did a subgroup analysis that excluded patients with cardiac arrest, the ultimate marker of physiologic exhaustion. Although perhaps clinically significant, mean cortisol levels were not statistically different in survivors from those who died from acute hemorrhage or its consequences. This is either caused by the low number of patients who died who had not suffered a cardiac arrest or that HAI is, in fact, simply a marker of depth of shock. Unfortunately, this study does not allow us to answer that question.

Even if HAI is simply a marker of depth of shock, it is a potentially treatable marker. Just as aggressive attempts to treat hypotension to maintain tissue perfusion once hemostasis is achieved and prevention or reversal of coagulopathy are mainstays of therapy in acute hemorrhage, perhaps treatment of HAI with steroids is warranted. In a hemorrhagic shock model, giving corticosterone to adrenalectomized rats decreased mortality.[37] In one human study of ICU patients requiring

vasopressors after hemorrhagic shock, administration of steroids increased vascular sensitivity regardless of the patient's response to a CST.[25] To begin to examine whether administration of steroids to acutely hemorrhaging patients may be beneficial, we performed a second subgroup analysis that excluded patients in whom anatomic hemostasis was simply never achieved and death resulted. As death following hemorrhage can be either the result of exsanguination or the consequence of hemorrhagic shock, we excluded patients who died of exsanguination because no adjunctive therapy will be helpful if hemostasis is not achieved. The remaining patients who died acutely of the sequelae of the hemorrhage did have significantly lower cortisol levels and would make up the subgroup of patients who would potentially benefit from administration of steroids.

This study is obviously limited by a number of factors. First, the fact that there is no nonhemorrhagic shock control group restricts our ability to draw definitive conclusions about the association with HAI and hemorrhage. The difficulty of doing this lies in finding an appropriate control cohort with similar physiological stresses. In addition, the fact that there were a small number of patients who did not have a cardiac arrest but died from hemorrhage greatly limits our ability to answer the vital question of whether HAI is simply a marker of shock or contributory to mortality.

Given that this is an observational study of a relatively small cohort of patients, this study may raise more questions than it answers. We think that determining the role of the HPA axis in acute hemorrhagic shock is an important area for future investigation. Further studies are certainly warranted to determine if steroid administration to hemorrhaging patients may be beneficial.

AUTHORSHIP

D.M.S., E.M.J., T.T., C.J.R., J.M., and T.M.S. designed this study. D.M.S. reviewed the literature. D.M.S., E.M.J., S.C., T.T., and C.J.R. collected the data, which D.M.S. and J.A.K. analyzed. D.M.S., E.M.J., J.A.K., T.T., C.J.R., J.M., and T.M.S. interpreted the data. D.M.S., E.M.J., J.A.K., J.M., and T.M.S. wrote the manuscript. D.M.S., E.M.J., J.A.K., T.T., C.J.R., J.M., and T.M.S. critically revised the article for publication.

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DISCLOSURE

The authors declare no conflicts of interest.

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DISCUSSION

Dr. Mihae Yu (Honolulu, Hawaii): When I started my career 30 years ago, adrenal insufficiency, or AI, in the critically-ill was not recognized. Some prominent members in this field questioned whether adrenal insufficiency truly existed.

We have come a long way. But the literature tends to be confusing for multiple reasons. The laboratory methodologies are heterogeneous, and there are over 60 definitions of adrenal insufficiency and failure. Furthermore, appropriate levels will vary with: 1) the disease process, 2) severity and duration of illness, 3) measurement of free, unbound, cortisol versus total cortisol, and 4) other un-measurable factors such as the level of glucocorticoid receptors.

One approach to this confusing topic is to be pragmatic: administering moderate doses of steroids appears to improve survival in patients with septic shock. That is the current recommendation: just give steroids to those who remain hypotensive after fluids if an underlying infection is suspected. But the preponderance of recent literature has focused primarily on septic patients and there is very little information in patients with hemorrhagic shock.

We welcome very much this study by Dr. Stein and colleagues who measured random total cortisol levels of patients in hemorrhagic shock as part of their initial trauma blood work. The authors wanted to answer the questions of whether AI exists acutely in this homogenous group of hemorrhagic shock patients, and whether the levels were related to outcome. The answer seems to be yes and yes. I just have a few questions for the authors.

Question number 1: Although the clinicians were blinded to the initial cortisol level, how many of the 43 patients who survived the first 24 hours developed hypotension or continued vasopressor requirement which prompted the clinicians to test them for adrenal insufficiency? I am particularly interested in the six patients who died later after the initial resuscitation. Were any of these patients retested for adrenal insufficiency and treated with steroids?

There are many definitions of adrenal insufficiency. The authors chose to define adrenal failure as <10 mcg/dL, and adrenal insufficiency as <25 mcg/dL. The authors found by their ROC curves that the best threshold was about 14.4 mcg/dL in predicting 24-hour mortality, and 18 mcg/dL in predicting in-hospital mortality. This is curious because the cortisol value of 15 mcg/dL or less and its association with mortality was one of the findings in the CORTICUS study done on septic shock patients (a multicenter trial).

Question number 2. Do the authors have recommendations on at what levels the patient should be treated? Or maybe because of the very high incidence of AI in this group of patients with hemorrhagic shock, 88% to be exact, should we adopt similar recommendations as in septic shock patients and just give moderate doses of steroids to those who remain hypotensive after the initial fluid and blood resuscitation?

I would like to thank the association for the opportunity to discuss this paper and I commend the authors for their significant contribution in better defining the role of cortisol in the early phase of hemorrhagic shock patients.

Dr. Rochelle A. Dicker (San Francisco, California): My question is a little bit along the lines of Dr. Yu. I am wondering if you did draw any free cortisol levels, keeping in mind that the definition of adrenal insufficiency is a little bit murky. Thanks.

Dr. Lawrence N. Diebel (Detroit, Michigan): Very nice presentation. A few questions.

First, in follow-up on these patients were any of them taking steroids exogenously? What is the half-life of cortisol in your body? And, third, on autopsy did anybody have bilateral adrenal hemorrhage?

Dr. Deborah M. Stein (Baltimore, Maryland): Thank you, Dr. Yu, for your comments and questions.

In answer to your first question, which was related to how many of these patients subsequently went on to develop adrenal insufficiency, particularly those patients who subsequently died while in the hospital, although survived their acute hemorrhage. We did not look at how many of those patients went on to develop it but certainly as we move forward with this work that is certainly something we will include in our future investigations.

With respect to how did we choose our levels, we went to the literature. As you stated, there are numerous definitions out there. We took a level of less than 10 as diagnostic of severe adrenal insufficiency based on the American College of Critical Care Medicine Consensus Statement. But certainly there are other levels that we could have picked.

The fact that the cut-off value of 14.4 is kind of interesting and I think I wouldn't make any recommendations about treatment in the setting of hemorrhagic shock at this time based on level but I think it's something that we need to look at again as we go forward.

As far as Dr. Dicker's question, we did not look at free cortisol for a variety of reasons. It's a lot more expensive and that was the main one. But we did look at total albumin levels that were drawn at the same time to make sure that the low total levels were not confounded by hypoalbuminemia.

And to Dr. Diebel's question, we did have one patient actually who was on steroids. He was excluded from the analysis which that was mentioned in the manuscript. His level was exceptionally low. He was a transplant patient that we didn't know about when we first drew his blood.

I don't know the half-life of cortisol in the body, to be honest with you. I mean we dose it every six to eight hours but I actually don't have that information.

I don't have any of the autopsy results but I can tell you that none of the patients had known adrenal hemorrhage. This was based on the several patients who did ultimately did undergo at least CT scan as well as obviously exploratory laparotomy.

I want to thank you very much for the privilege of the podium and I hope you all enjoy the sunshine. Thank you.