Cortisol Levels and Corticosteroid Administration Fail to Predict Mortality in Critical Illness

The Confounding Effects of Organ Dysfunction and Sex

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Background: Corticosteroid supplementation based on plasma cortisol measurement was reported to decrease mortality in vasopressor-dependent critical illness.

Hypothesis: Random levels or maximal increments of plasma cortisol measured after short adrenal stimulation may predict mortality independent of concurrent organ dysfunction or sex, and corticosteroid supplementation may decrease mortality in vasopressor-dependent critical illness.

Design: An observational descriptive study.

Patients: Critically ill patients receiving vasopressors for treatment of hemodynamic instability.

Methods: Random levels (n=522 patients) and maximal increments (n=282 patients) of plasma cortisol were measured after 250 µg of adrenocorticotropic hormone was administered for short stimulation tests before patients received corticosteroid supplementation. The severity of acute illness was measured by sequential organ failure assessment.

Main Outcome Measure: Hospital mortality.

Results: The overall mortality was 24%. A random plasma cortisol level of 15 µg/dL or less was associated with lower mortality than a random plasma cortisol level greater than 15 µg/dL in men (12% vs 26%, respectively; P<.01) and women (13% vs 31%, respectively; P<.01). A maximal plasma cortisol increment of 9 µg/dL or less increased mortality as compared with an increment greater than 9 µg/dL in men (31% vs 11%, respectively; P<.01) but not in women (30% vs 29%, respectively; P=.8). Random levels and maximal increments of plasma cortisol did not influence hospital mortality predicted by the sequential organ failure assessment score. Corticosteroids were given to 244 patients (47%) without an effect on mortality (mortality rate of 27% for patients given corticosteroids vs mortality rate of 22% for patients who did not receive corticosteroids; P=.6). Corticosteroids did not influence mortality when plasma cortisol was a random level of 15 µg/dL or less (mortality rate of 14% for patients who received corticosteroids vs mortality rate of 10% for those who did not receive corticosteroids; P=.4) or when plasma cortisol was a maximal increment of 9 µg/dL or less (mortality rate of 30% for patients who received corticosteroids vs mortality rate of 31% for patients who did not receive corticosteroids; P=.9).

Conclusions: Remote organ dysfunction and sex influenced mortality associated with cortisol levels measured in critical illness. Corticosteroid supplementation guided by arbitrary levels or increments of plasma cortisol in critical illness did not improve survival. Better guidelines for corticosteroid supplementation in critical illness should be developed to avoid potential adverse effects from unwarranted treatment.

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Prognostic classification for adrenal abnormalities, based on random levels and maximal increments of plasma cortisol after administration of exogenous adrenocorticotropic hormone (ACTH) for septic shock, has been described.1 Blunted adrenal cortisol output and low random levels were reported to increase mortality in critically ill patients. Relative cortisol deficiency was proposed to explain the abnormalities of plasma cortisol levels when associated with hemodynamic instability and vasopressor dependency in acute critical illness.2-4 Subsequently, a small randomized control trial reported a survival benefit from corticosteroid supplementation in vasopressor-dependent septic shock.5

See Invited Critique at end of article

There is no consensus agreement regarding the existence or the definition of relative cortisol deficiency in the criti-
cally ill. The extent of disagreement among different clinical studies was highlighted by the wide range for plasma cortisol cutoff levels (range, 15-34 µg/dL) used to define cortisol deficiency and to trigger exogenous supplementation in vasopressor-dependent critical illness.\(^1^6-11\)

Other investigators disagreed about whether plasma cortisol increments should be measured after a low (1-µg) or high (250-µg) dose of ACTH to unmask the relative cortisol deficiency.\(^6,12-14\) With that background of controversies in the published literature, the current study was performed to test the hypothesis that random levels or maximal increments of plasma cortisol may predict mortality independent of concurrent organ dysfunction or sex, and corticosteroid supplementation may decrease mortality in vasopressor-dependent critical illness. The design was an observational descriptive study conducted at a single tertiary care institution.

## METHODS

### STUDY POPULATION

The study was performed at a tertiary care teaching hospital. The institutional review board approved the study. Mayo Clinic Hospital (Scottsdale, Ariz) is a 250-bed tertiary care teaching hospital. Patients were admitted to a 20-bed multidisciplinary (medical, surgical, and coronary care) closed intensive care unit. The study cohort consisted of adult patients who were admitted to the Mayo Clinic Hospital intensive care unit between January 1, 1999, and December 31, 2003. Patients were eligible for the study if they met the following criteria: (1) had persistent hypotension (mean arterial pressure of ≤60 mm Hg) after adequate volume resuscitation to central venous pressure between 12 and 15 mm Hg;\(^1^5\) (2) required initiation of vasopressor therapy and continued the therapy for more than 24 hours; (3) met 2 or more criteria for systemic inflammatory response syndrome;\(^1^\) (4) had documented or clinical suspicion of infection and required antibiotic therapy for greater than 3 days; (5) had not received exogenous corticosteroids before admission; and (6) had cortisol measurements obtained prior to corticosteroid administration. The vasopressor agents, with corresponding dose ranges, used in the study were norepinephrine (0.05-5.0 µg/kg per minute), phenylephrine (0.3-6.0 µg/kg per minute), epinephrine (0.01-7.0 µg/kg per minute), dopamine (6-30 µg/kg per minute), and vasopressin (0.04-0.4 U/min). Patients who had already received corticosteroids or who did not undergo cortisol measurements prior to supplementation were excluded from the study. All patients were managed by in-house intensivists (critical care attending staff physicians), except for coronary care patients for whom critical care consultation was provided with the primary care of cardiologists.

### CORTISOL MEASUREMENTS AND TREATMENT

Plasma cortisol measurements were performed while patients were receiving vasopressor therapy within 24 hours of admission to the intensive care unit.

A short ACTH stimulation test was performed with 250 µg of cosyntropin (Cortrosyn; Amphastar Pharmaceuticals, Rancho Cucamonga, Calif) given as an intravenous bolus over 2 minutes. Blood samples were obtained immediately before the test and at 30 and 60 minutes afterward. After centrifugation, plasma samples were stored at 4°C and total plasma cortisol levels were determined with a commercially available chemiluminescent immunoassay kit (Roche Diagnostics Corporation Inc; Indianapolis, Ind) within 2 hours of sampling. The cortisol increment was defined as the difference between the level immediately before the test and the highest of the concentrations at 30 and 60 minutes.

After obtaining blood samples, patients were treated at the discretion of the intensivist with an initial dose of 100 mg of hydrocortisone administered intravenously 3 times daily. After discontinuation of vaspressors, infusions, and reversal of hypotension, the dose of corticosteroid supplementation was decreased to 50 mg administered intravenously 3 times daily for 4 days and then was maintained at 50 mg administered intravenously twice per day until recovery from the acute critical illness. The rationale for this particular dosage regimen was to avoid adverse effects from prolonged exposure to high doses of corticosteroids. None of the study patients received fludrocortisone supplementation.

### DATA COLLECTION

Information about demographics, preadmission comorbidities, type and reason for admission, intensive care interventions and treatment, acute diagnosis, and death during hospital stay was obtained from electronic medical records. Data were extracted from electronic medical records into an institutional clinical database. Severity of acute illness in the intensive care unit was determined by the sequential organ failure assessment (SOFA) score.\(^1^6\) The SOFA score was calculated based on graded severity of dysfunction of 6 organ systems (neurological, pulmonary, cardiovascular, hepatic, renal, and coagulation). The SOFA score was derived from daily laboratory data, vital signs, and medication infusion information stored in a Structured Query Language electronic database.\(^1^7\) The maximal daily SOFA score was determined for the entire stay in the intensive care unit.

### STATISTICAL ANALYSIS

All continuous variables were presented as median (10th-90th percentile range) and were analyzed by t test or Wilcoxon rank sum test when appropriate. Categorical variables were expressed as actual numbers as well as percentages, and they were analyzed by χ² or the Fisher exact test as appropriate. Nonparametric tests of the median (number of points above median) were performed where appropriate for comparison of length of stay. Hospital death was the dependent or primary outcome variable. The cutoff levels for random levels and maximal increments of plasma cortisol to predict mortality and to recommend corticosteroid supplementation as published in previous landmark papers\(^1^3,6,10,13,14\) were reevaluated in this study. The cutoff for the maximal daily SOFA score was determined by a likelihood ratio test. Multiple logistic regression was performed to determine the prediction model for hospital mortality using the threshold for plasma cortisol and the SOFA score. Calibration of the logistic model was examined by the Hosmer-Lemeshow goodness-of-fit test to evaluate the importance of the discrepancy between observed and expected hospital mortality. Discrimination of the logistic model was examined by the area under the receiver operating characteristic curve to evaluate how well the model distinguished risk of hospital death for individual patients. A receiver operating characteristic curve was constructed by plotting the sensitivity vs (1-specificity) of the factors associated with death. All statistical tests were 2-tailed and significance was accepted at P<.05. Statistical analysis was performed using JMP statistical software, version 5.1 (SAS Institute Inc, Cary, NC).
RESULTS

COHORT DESCRIPTION

During the study period, 7241 patients were admitted to the intensive care unit and 484 (6%) died in the hospital. Vasopressor therapy was initiated in 3286 patients, of whom 522 patients met the inclusion criteria of the study and had plasma cortisol measurements obtained. Of all patients receiving vasopressor therapy, 2343 patients did not receive corticosteroids (median SOFA score 6 [range, 2-9], mortality 7%) and 943 patients were given corticosteroid supplementation (median SOFA score 7 [range, 3-12], mortality 17%; $P < .01$).

Of the patients included in the study, 128 (24%) subsequently died in the hospital. There were 63 women who died at a median of 8 days (range, 1-31 days). There were 65 men who died at a median of 7 days (range, 1-30 days).

Table 1 and Table 2 describe demographics, preadmission comorbidities, admission type and reason, clinical site of infection, antibiotic coverage, interventions, and complications, stratified by sex and hospital survival. Liver disease and malignancy were common in nonsurvivors. The respiratory, abdominal, and genitourinary areas constituted more than 75% of clinically suspected infectious sites in these patients. Cultures of suspected sites performed on admission yielded positive results in half of the study patients. Antibiotics for gram-negative bacterial infection were most commonly used, particularly in female nonsurvivors. Antifungal therapy was more frequently used in nonsurvivors of both sexes. Nonsurvivors had more frequent pulmonary artery catheterization and mechanical ventilation than survivors. Median blood glucose levels on admission, first...
day SOFA scores, and maximal daily SOFA scores (with and without cardiovascular scores included) were higher in nonsurvivors of both sexes. There were more female nonsurvivors who required vasopressor therapy for more than 72 hours. Corticosteroid supplementation was similar among survivors and nonsurvivors. With regard to complications, the only distinctive difference was a higher incidence of acute renal failure among nonsurvivors. Hospital length of stay was also shorter for nonsurvivors of both sexes.

**SEX DIFFERENCES FOR PLASMA CORTISOL RESPONSE AND MORTALITY**

Random plasma cortisol levels were measured in 522 patients (230 women and 292 men) while they were receiving vasopressor therapy. Short ACTH stimulation tests were performed in 282 patients (119 women and 163 men). Corticosteroid supplementation was initiated in 244 patients (47%; Table 2). Vasopressor therapy for more than 72 hours was seen in 36 patients (15%) who received corticosteroids and 33 patients (12%) who did not receive corticosteroids (P = .4).

Table 3 describes the outcome associated with different thresholds of random or stimulated plasma cortisol output for women and men. Random plasma cortisol levels below the different quoted thresholds were associated with lower mortality for women and men. Stimulated plasma cortisol increments of 9 µg/dL or less were associated with 3-fold higher mortality in men only. Women with cortisol increments of 9 µg/dL or less had a median SOFA score of 9 (10th-90th percentile range, 4-14), and those with increments greater than 9 µg/dL had a median SOFA score of 17 (10th-90th percentile range, 13-21), at P < .01. The mortality rates for women with either increments of 9 µg/dL or less or increments greater than 9 µg/dL were high. Women with cortisol increments of 9 µg/dL or less had a median SOFA score of 9 (10th-90th percentile range, 4-14), and those with increments greater than 9 µg/dL had a median SOFA score of 17 (10th-90th percentile range, 13-21), at P < .01. The mortality rates for women with either increments of 9 µg/dL or less or increments greater than 9 µg/dL were high.

**INTERACTION OF ORGAN AND ADRENAL DYSFUNCTION WITH MORTALITY**

The effect of SOFA scores and different thresholds for random levels of plasma cortisol and increments measured after adrenal stimulation on hospital mortality is depicted in Table 4. On multivariate analysis with SOFA scores, random plasma cortisol levels below different thresholds were associated with lower mortality, and basal plasma cortisol levels greater than 34 µg/dL and stimulated increments of 9 µg/dL or less had the highest mortality. Men who had basal plasma cortisol levels of 34 µg/dL or less and stimulated increments of greater than 9 µg/dL had the lowest mortality.

**Table 2. Interventions and Complications for the Study Cohort**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Survivors (n = 227)</th>
<th>Nonsurvivors (n = 65)</th>
<th>Survivors (n = 167)</th>
<th>Nonsurvivors (n = 63)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary artery catheterization</td>
<td>107 (47)</td>
<td>37 (57)†</td>
<td>60 (36)</td>
<td>29 (62)†</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>117 (52)</td>
<td>47 (72)†</td>
<td>78 (47)</td>
<td>41 (65)†</td>
</tr>
<tr>
<td>Admission SOFA score‡</td>
<td>8 (3-12)</td>
<td>10 (4-15)†</td>
<td>6 (3-11)</td>
<td>10 (5-14)†</td>
</tr>
<tr>
<td>Maximal daily SOFA score excluding</td>
<td>5 (1-10)</td>
<td>8 (5-12)†</td>
<td>5 (1-8)</td>
<td>9 (3-12)†</td>
</tr>
<tr>
<td>Vasopressor therapy &gt;72 h</td>
<td>29 (13)</td>
<td>10 (13)</td>
<td>15 (9)</td>
<td>12 (19)†</td>
</tr>
<tr>
<td>Corticosteroid supplementation</td>
<td>104 (46)</td>
<td>33 (51)</td>
<td>73 (44)</td>
<td>34 (54)</td>
</tr>
<tr>
<td>Neurorlogical complications</td>
<td>44 (25)</td>
<td>17 (26)</td>
<td>36 (27)</td>
<td>12 (17)</td>
</tr>
<tr>
<td>Acute gastrointestinal hemorrhage</td>
<td>10 (4)</td>
<td>4 (6)</td>
<td>7 (4)</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>54 (24)</td>
<td>28 (43)†</td>
<td>33 (20)</td>
<td>30 (48)†</td>
</tr>
<tr>
<td>Nosocomial infections</td>
<td>134 (59)</td>
<td>44 (68)</td>
<td>106 (63)</td>
<td>47 (75)</td>
</tr>
<tr>
<td>Postoperative complications</td>
<td>78 (34)</td>
<td>18 (28)</td>
<td>38 (23)</td>
<td>21 (33)</td>
</tr>
<tr>
<td>ICU stay, d‡</td>
<td>3 (1-14)</td>
<td>3 (1-13)</td>
<td>3 (1-16)</td>
<td>3 (1-19)</td>
</tr>
<tr>
<td>Hospital stay, d‡</td>
<td>11 (3-35)</td>
<td>7 (1-30)†</td>
<td>11 (3-32)</td>
<td>8 (1-31)†</td>
</tr>
</tbody>
</table>

Abbreviations: ICU, intensive care unit; SOFA, sequential organ failure assessment.
*Values are number (percentage) unless otherwise indicated.
†P < .01 for nonsurvivors vs survivors.
‡Values are median (10th-90th percentile range).

Table 4 illustrates the study cohort characteristics and outcome associated with supplementation with corticosteroids. Age, sex, and SOFA scores were similar in patients with and without corticosteroid supplementation. Patients with random plasma cortisol levels of 15 µg/dL or less, or with stimulated cortisol increments of 9 µg/dL or less, were more likely to receive corticosteroid supplementation. The length of stay and survival were

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similar in both groups of patients. Characteristics of non-survivors from both groups of patients were similar, except for higher mortality for patients who had basal plasma cortisol levels greater than 34 µg/dL and stimulated cortisol increments of 9 µg/dL or less and had received corticosteroid supplementation.

The salient findings of the study were the following: (1) random plasma cortisol levels below the thresholds reported in the literature as triggers for corticosteroid replacement were already associated with low mortality without corticosteroid supplementation; (2) remote organ dysfunction determined the mortality attributed to measured plasma cortisol levels; (3) sex influenced mortality associated with measured plasma cortisol levels; and (4) corticosteroid supplementation did not decrease mortality in vasopressor-dependent critical illness.

The study could be criticized for being retrospective and nonrandomized in design; however, the report findings were still significant as the study represented a typi-
In acute critical illness, the interpretation of plasma cortisol levels as an indicator of cortisol deficiency was solely based on vasopressor dependency and hemodynamic improvement after corticosteroid supplementation.
tion. Exogenous corticosteroids were shown to possess vasopressor activity by augmentation of arteriolar smooth muscle vasoconstriction induced by catecholamines irrespective of endogenous levels of cortisol. In the current study, corticosteroid supplementation did not influence vasopressor dependency beyond 72 hours. These findings suggest that vasopressor dependency is not necessarily a criterion for cortisol deficiency but a manifestation of peripheral interactions between endogenous vasodilators and circulating cytokines in these patients. Vincent et al reported similar findings to indicate that the widespread use of corticosteroid supplementation in septic shock did not translate into either a change in vasopressor requirement or restoration of hemodynamic stability.

Better clinical indicators should be employed to understand the relevancy of measured plasma cortisol levels in conjunction with the host hormonal milieu to avoid unwarranted corticosteroid supplementation. Clinical indicators from glucose metabolism, electrolyte balance, inflammation, organ recovery, and surrogate markers of hormonal feedback regulation would be superior markers to ascertain absolute cortisol deficiency. Manglik et al used serum electrolytes and glucose levels as an adjunct to measured plasma cortisol levels to confirm primary adrenal failure and to guide replacement therapy. When stringent clinical criteria were applied in the critically ill, corticosteroid supplementation was required in less than 4% of patients receiving vasopressor therapy without adverse outcome. In the current study, patients who received corticosteroid supplementation had elevated blood glucose levels at admission and refuted the presence of absolute cortisol deficiency irrespective of measured plasma cortisol levels. Perhaps that would also account for the lack of survival benefit from corticosteroid supplementation seen in these patients. Future guidelines should address the role of adjunct clinical criteria other than vasopressor dependency before deciding on corticosteroid supplementation in the critically ill.

Hamrahian et al indicated that the ratio of free cortisol to plasma protein–bound cortisol was altered in these patients in the face of changing protein binding capacity. Sex hormones, known to influence plasma protein binding for endogenous cortisol, could also influence the ratio of free cortisol to protein-bound cortisol in women and men. Therefore, the sex differences for adrenal cortisol output and clinical outcome might reflect differences in free cortisol availability.

RELATIONSHIP OF ADRENAL AND REMOTE ORGAN DYSFUNCTION WITH MORTALITY

This study shows that the severity of concurrent organ dysfunction is the principal risk factor for hospital death. When stratified by the SOFA score, neither plasma cortisol levels nor corticosteroid supplementation determined mortality. The conclusions were the same whether the cardiovascular score was included or excluded from the SOFA score, confirming that remote organ dysfunction, besides the cardiovascular system, predicted hospital mortality. Bouachour et al reported a similar association of organ dysfunction with mortality independent of plasma cortisol levels. Autopsy findings from Soni et al revealed intact adrenal gland cortices in descendents diagnosed with relative adrenal insufficiency and multiple organ failure. That would suggest that functional alteration of adrenal cortex was secondary to the host humoral milieu associated with development of multiple organ dysfunction and should be viewed as an epiphenomenon rather than a causation. Annane et al reported that plasma cortisol levels predicted mortality independent of remote organ failure in the critically ill. The superior performance of the SOFA score to measure the severity of remote organ dysfunction compared with the traditional classification of failing organs as all-or-none could explain the difference between the current study and that of Annane et al. The findings have implications for the design of future clinical trials intended to address survival benefits from corticosteroid supplementation in the presence of multiple organ dysfunction.

EFFECT OF CORTICOSTEROID SUPPLEMENTATION

Although corticosteroid supplementation was given to half of the study cohort, we could not detect any reduction in hospital mortality from such treatment among the different subgroups defined by sex, severity of organ dysfunction, presence of infection, and random levels or maximal increments of plasma cortisol. While the study could not define any specific morbidity linked to corticosteroid use among patients enrolled in the study, it was noted that the overall mortality of patients receiving vasopressors with corticosteroid supplementation (but who were excluded from the study because of initiation of treatment without prior cortisol measurements) was much higher at 17% compared with 7% without supplementation during the same study period. The group of patients not enrolled in the study who were receiving vasopressors with corticosteroid supplementation also had much higher SOFA scores, which explains the increased mortality. That observation in the larger cohort confirmed that concurrent organ dysfunction, and not necessarily corticosteroid supplementation, was the determinant of mortality seen in the enrolled study patients. However, within the limitation of the current study, the cause-and-effect relationship between corticosteroid supplementation and increased mortality for the larger cohort could not be addressed because of a lack of treatment randomization.

SEX DIFFERENCES FOR MORTALITY ASSOCIATED WITH ADRENAL DYSFUNCTION

An unusual finding of the study was the sex differences for the prognosis of adrenal cortisol output after short ACTH stimulation. A blunted cortisol increment was associated with a 3-fold increase of mortality in men and was also related to higher SOFA scores in that group. However, the mortality rate for women irrespective of the cortisol increment was much higher than that for men with normal ACTH stimulation. The high mortality rate in
women with normal and blunted short ACTH stimulation was explained by high median SOFA scores in both groups. Perhaps the threshold often quoted in the literature for a cortisol increment of 9 µg/dL had no prognostic value in women with concurrent multiple organ dysfunction. Recent studies22,23,24 reported overproduction of estrogens and glucocorticoids in relation to androgens by adrenal cortex at an early stage of critical illness. Further work is necessary to clarify the sex differences of outcome related to different patterns of sex hormones and cortisol production.

STUDY LIMITATIONS

The study has several limitations. The patient case mix included circulatory failure secondary to systemic inflammatory response and was not confined to septic shock. However, the case mix reflected the spectrum of critical illness commonly encountered in clinical practice. The overall mortality was low (24%) compared with previous studies,1,5,8 which could also explain the lack of benefit from corticosteroid supplementation under these circumstances. The lack of association between cortisol measurements and mortality might also be related to the use of total (free and protein-bound) plasma cortisol levels instead of free plasma cortisol levels in the study cohort. The ratio of free to bound cortisol reportedly increases, so that even normal or low levels of total plasma cortisol were associated with elevated levels of free plasma cortisol in critical illness.23 Another potential limitation was the exclusion of patients who received corticosteroid supplementation without prior cortisol measurements from the study. The exclusion of these patients was necessary to address the prognostic implications of measured plasma cortisol levels and subsequent supplementation on clinical outcome.

In conclusion, remote organ dysfunction and sex had confounding effects on mortality associated with cortisol levels in vasopressor-dependent critical illness. Corticosteroid supplementation guided by arbitrary cutoff levels or increments of plasma cortisol had no survival benefit in these patients. Guidelines for corticosteroid use of total (free and protein-bound) plasma cortisol increments, so that even normal or low levels of total plasma cortisol were associated with elevated levels of free plasma cortisol in critical illness.23 Another potential limitation was the exclusion of patients who received corticosteroid supplementation without prior cortisol measurements from the study. The exclusion of these patients was necessary to address the prognostic implications of measured plasma cortisol levels and subsequent supplementation on clinical outcome.

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