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*Original Article*

# Hypoadrenalism Following Trauma: Is Sepsis Always Necessary?

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**Abstract**: *Purpose of the Study*: Trauma patients can exhibit the systemic inflammatory response syndrome (SIRS) without evidence of infection. SIRS from infection has been associated with hypoadrenalism. We hypothesized that hypoadrenalism can accompany SIRS from trauma without infection. To investigate this further, we performed a retrospective study of trauma patients admitted to the ICU at our rural academic level 1 trauma center from October 2003- June 2005, with measurement of blood cortisol in the first 7 days after injury (N=33). We determined the incidence of hypoadrenalism based on serum cortisol levels and performed a univariate analysis to delineate factors associated with hypoadrenalism. *Significant Findings*: Twelve of 33 (36.6 %) were diagnosed with hypoadrenalism on mean ICU day 2.8. SIRS was documented in 92% of hypoadrenal patients *vs.* 52% of patients without hypoadrenalism (p=0.021). No patient had evidence of invasive infection. Younger age and higher ISS were also associated with hypoadrenalism. There were no gender differences identified, although most patients in the study were male. There was a trend toward higher etomidate use in the hypoadrenal group, although this was not statistically significant. *Conclusions*: Trauma patients who demonstrate SIRS early in their ICU course may exhibit hypoadrenalism without infection. Younger age and higher ISS also appear to be associated with this alteration. Further study is needed to determine the true incidence of this condition, and to better delineate which trauma patients are most susceptible.

**Key Words:** Hypoadrenalism, trauma, sepsis, sirs, etomidate

## Introduction

The study of adrenocortical function in the critically ill dates back as early as 1915, when Corbett described suprarenal exhaustion in shock patients [1,2]. Blood cortisol concentrations have since been shown to increase in response to insults such as trauma, burns, cardiac arrest, infection, and surgery, with concentrations of 25-30μg/dl commonly measured [1,3]. In this setting, the circadian rhythm of higher cortisol levels in the morning compared to the evening is replaced with an elevated concentration 24 hours per day [1].

Many reports have documented blood cortisol concentrations lower than expected during critical illness [1,3,9], a condition commonly termed "relative adrenal insufficiency." Recent literature suggests that the incidence of such hypoadrenalism in the critically ill may as high as 40% during septic shock [4,5,6,10]. Importantly, treatment of septic hypoadrenal patients with physiologic doses of hydrocortisone and fludrocortisone has been shown to improve survival [9].

Although the concept of hypoadrenalism during sepsis is now widely accepted, it is unknown whether hypoadrenalism is manifested in other types of severe inflammatory conditions. Sepsis is defined as the presence of the systemic inflammatory response syndrome (SIRS [10]), with an invasive infection [10]. Many trauma patients meet the definition of SIRS shortly after injury, before invasive infection is evident [11]. Since infection is not a necessary etiology of severe systemic inflammation, it is possible that the

inflammatory response, rather than infection, may be the key element in development of hypoadrenalism in the critically ill. We hypothesized that hypoadrenalism may occur in critically injured patients who manifest SIRS in the absence of sepsis.

## Materials and Methods

We performed a retrospective study of all trauma patients admitted to the intensive care unit (ICU) in our rural level I academic trauma center from October 2003 to June 2005 who had cortisol measured (N=50). Patients were excluded if the first cortisol was drawn after ICU day 8 (n=10), or if they exhibited evidence of sepsis (physiologic criteria for SIRS, and culture evidence of infection) (n=7). None of the patients had a prior history of adrenal insufficiency, or recent treatment with exogenous steroids. Data abstracted on the remaining 33 patients included age, injury severity score (ISS), ICU length of stay, etomidate use, and basal as well as stimulated cortisol concentrations (ACTH stimulation test) when available. The ACTH stimulation test consisted of obtaining a basal serum cortisol followed by an additional level 30-60 minutes after the intravenous administration of 250μg of cosyntropin. Hypoadrenalism was defined as: basal cortisol <15μg/dl and/or cortisol increase < 9μg/dl following 250μg cosyntropin [1,3,12]. A basal serum cortisol value of ≥ 30μg/dl precluded a diagnosis of hypoadrenalism regardless of the ACTH stimulation test [1,3,12]. There is no guideline at our institution to state which patients should have cortisol levels or an ACTH stimulation test performed. The decision was at the discretion of the ICU team based on clinical parameters that, in retrospect, are impossible to precisely delineate.

Physiologic criteria defining SIRS [10] (temperature, pulse, respiratory rate, PCO2, white blood cell count) were recorded at the time that cortisol measurements were obtained. We reviewed all available culture data for each patient during the defined study period (Day 1-8). Infection was defined as any positive culture obtained during the days studied. All cultures were performed at the discretion of the primary treatment team.

We identified a subset of patients with head injury, and recorded GCS and type of injury in addition to the other patient variables mentioned above.

Student's *t*-test was used for analysis of continuous variables. $Chi^2$ tests were used for categorical variables. All statistical analyses were performed using STATA version 8.2 software (College Station, TX). P-values of < 0.05 were considered statistically significant. All p-values are two-tailed values. This study was approved by our institution's internal review board (IRB).

## Results

Twelve of the 33 patients (36.6%) were diagnosed with hypoadrenalism on mean ICU day 2.8. Two of the patients had basal cortisol levels below 15μg/dl. Ten patients were diagnosed based on an inadequate response to 250μg cosyntropin (less than 9μg/dl increase). Patient demographics are highlighted in **Table 1**. The hypoadrenal patients were younger (39.6 *vs.* 59.2 years), had higher ISS (26.0 *vs.* 20.9), and were more

**Table 1**: Patient Demographics in the Study Group (33 patients)

| | Overall | Hypoadrenal (n=12) | Not Hypoadrenal (n=21) | p-value |
|---|---|---|---|---|
| Age Mean (+/- SD) | 49.5y (20.5) | 39.6y (21.1) | 59.2y (18.3) | 0.033 |
| ISS Mean (+/- SD) | 22.7 (7.5) | 26.0 (7.8) | 20.9 (6.8) | 0.050 |
| ICU Days Mean (+/- SD) | 14.4 (13.1) | 19.3 (13.0) | 11.6 (12.5) | 0.107 |
| Race (% White) | 96.97% | 100% | 95.24% | 0.589 |
| Gender (% Male) | 72.7% | 75.0% | 71.4% | 0.825 |
| Head Injury | 30.3% | 33.3% | 28.6% | 0.775 |
| Etomidate | 45.5% | 66.7% | 33.3% | 0.067 |
| SIRS | 66.7% | 91.7% | 52.4% | 0.021 |

Table 2: Patient Demographics in Those with Head Injury

| Case # | Age/Sex | ISS | GCS | Injury Type | Hypoadrenal | Etomidate | SIRS |
|---|---|---|---|---|---|---|---|
| 1 | 41m | 21 | 3T | SDH/SAH | No | No | No |
| 2 | 19m | 27 | 15 | IPH/SAH | No | No | Yes |
| 3 | 41m | 29 | 14 | SDH | No | Yes | Yes |
| 4 | 49m | 30 | 3T | EDH/SDH | No | No | Yes |
| 5 | 68f | 9 | 9T | SDH | No | Yes | No |
| 6 | 34m | 24 | 3T | IPH | Yes (Day 1) | No | Yes |
| 7 | 63f | 16 | 13 | IPH | No | No | No |
| 8 | 29f | 45 | 10 | SAH/DAI | Yes (Day 1) | Yes | Yes |
| 9 | 54m | 26 | 3T | SDH | Yes (Day 6) | Yes | Yes |

EDH (epidural hematoma), SDH (subdural hematoma), SAH (subarachnoid hematoma), DAI (diffuse axonal injury), IPH (intraparenchymal hemorrhage)

likely to exhibit SIRS (91.7% *vs.* 52.4%). There was a trend toward higher etomidate use in the hypoadrenal group, along with a longer ICU stay, and higher incidence of head injury, although these were not statically significant.

The cohort of head injury patients is shown in Table 2. Three of 9 patients were diagnosed with HA, all exhibited SIRS.

Univariate analysis was performed using chi square tests to determine factors associated with hypoadrenalism. Age 40 or less ($p = 0.006$), ISS>20 ($p=0.047$), and the presence of SIRS ($p=0.021$) were significant predictors of hypoadrenalism. There was a trend toward a higher incidence of hypoadrenalism in the group who received etomidate ($p =0.064$), but this did not reach statistical significance. There was no difference in the incidence of hypoadrenalism between male and female gender, those with head injury, or those with ISS scores above 20.

A multivariate logistic regression analysis was performed to account for factors with a p-value < 0.20. Age less than 40, SIRS, etomidate, and ISS greater than 20 were entered into the model. The model was unable to isolate any single factor as being associated with hypoadrenalism.

## Discussion

Our data demonstrates that hypoadrenalism can be evident without evidence of infection in patients who exhibit SIRS following injury. Younger age also appears to be associated with this alteration.

In this study, 45.5% of the patients received a single dose of etomidate in the field for intubation by the emergency transport team. The hypoadrenal patients had a higher incidence of etomidate use, but this did not reach statistical significance. Etomidate is a popular induction agent for intubation in trauma patients due to its rapid onset, cardiovascular stability, and absence of respiratory suppression. Etomidate is known to suppress adrenocortical function by inhibition of 11-β-hydroxylase, thus decreasing cortisol synthesis [12,22]. A single dose of etomidate has been shown to impact adrenal function in up to 88% of patients [18]. This effect appears to occur early after the dose is received and has been shown to last approximately 4-8 hours, at which point, adrenal function appears to be equal to that of control subjects [12,22]. The mean day of diagnosis of hypoadrenalism in our study was day 2.8 after injury. It is possible that some of the patients diagnosed on day 1 may have had some residual effect from etomidate, however, it is less likely that etomidate is the principle etiology of hypoadrenalism in the majority of patients (who were diagnosed greater than 2 days into their course). This study lacks the statistical power to definitively prove or disprove the role of etomidate in hypoadrenalism in this cohort of patients. This subject deserves prospective study to determine the true incidence of hypoadrenalism on arrival in patients who received etomidate, the period of time before return of normal adrenal function, and whether this hypoadrenalism has any adverse outcomes associated with it.

Nine of the patients suffered head trauma. Of these, 3 exhibited hypoadrenalism (Table 2). This association with head trauma is similar to

that shown by Cohan *et al* [11], who reported a 50% incidence of hypoadrenalism in patients with traumatic brain injury (TBI) in their prospective study. Also, similar to our results, Cohan reports an association of hypoadrenalism with younger age and higher injury severity scores in their TBI patients. In that study, hypoadrenalism was also associated with higher frequency of early ischemic insults (hypoxia, hypotension, severe anemia), lower trough blood pressures, and higher need for vasopressor use, all of which may be associated with severe systemic inflammation separate from head trauma. Further study is required to determine if these associations are also observed in a general trauma population that is broader than TBI alone.

There are several limitations to this study. First, the number of patients studied is relatively small. Based on this information, we are unable to draw any conclusions about which subsets of trauma patients are at greatest risk for hypoadrenalism. The small study size also limits our ability to perform multivariate analysis to better investigate the interactions between variables associated with hypoadrenalism. A larger sample size will be required to help delineate these interactions. It is impossible to retrospectively determine what was or was not different about the 50 patients who had cortisol levels drawn, and why the primary team chose to investigate their adrenal function. This remains a major limitation of this study, and supports the need for prospective study of this subject. There was also no way to retrospectively determine a culture strategy for these patients. All cultures were ordered at the discretion of the primary team. This is typically done in patients with new onset fever, or unexplained increasing white blood cell count, but we were not able to determine why cultures were ordered on individual patients. We determined any patient with a positive culture and SIRS to have sepsis, and excluded them from analysis, although some of those patents may have simply had colonization rather than true infection.

In conclusion, hypoadrenalism can develop following serious injury without obvious infection. Further study is necessary to better determine the incidence and risk factors (ie etomidate, SIRS, etc.) of this condition. Finally, much more investigation will be necessary to determine if cortisol replacement is beneficial for hypoadrenalism in severe trauma.

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