Adrenal insufficiency in critically ill septic patients at Dr George Mukhari Hospital

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Abstract
Rationale: Adrenal insufficiency occurs with varying frequency in critically ill patients. It is usually associated with a high mortality and poor clinical outcome. Objective: To determine the incidence of adrenal failure in patients with severe sepsis and septic shock admitted to our intensive care unit. Design: Prospective observational study, over a two year period (June 2003 – June 2005). Setting: University hospital multi-disciplinary intensive care unit in South Africa. Patients: One hundred and fifty-two patients with severe sepsis and septic shock. Patients with a history of adrenal insufficiency, those on steroid therapy and all those who received etomidate within a week prior to enrollment were excluded. Interventions: None.
Measurements and main results: A random plasma cortisol level was measured in consecutive patients with severe sepsis and septic shock. Adrenal insufficiency was defined as a cortisol level below 20µg/dL. The incidence of adrenal insufficiency was 26.97% (CI: 19.97% - 34.03%). Patients with adrenal insufficiency had lower APACHE II scores and better short-term survival rates. The occurrence of adrenal dysfunction in patients with septic shock was low with an incidence of 15.6%. The type of infecting organism, site of infection and the origin of the sepsis were not associated with differences in the incidence of adrenal deficiency. Conclusion: Absolute adrenal insufficiency is not uncommon among our critically septic patients. The presence of adrenal failure was inversely correlated with illness severity and mortality.

Keywords: Adrenal insufficiency, Cortisol, Sepsis.
Methods
This was prospective, observational study over a two year period (June 2003 and June 2005).
Consecutive adult subjects aged more than 17 years with severe sepsis or septic shock on admission to the ICU or developing these clinical diagnoses during their stay in the ICU formed the study population. Severe sepsis or septic shock was defined according the American College of Chest Physicians/Society of Critical Care Medicine consensus conference criteria. The following data was recorded on all subjects: demographic details, vital signs, Inotropic support, site of sepsis, short-term (ICU) mortality rate, illness severity (APACHE II score), microbiological isolates and the length of stay in the intensive care unit. Plasma cortisol concentrations were determined by chemiluminescent immunoassay. Absolute adrenal insufficiency was defined by a random cortisol level of <20 µg/dl. Patients with a history of adrenal insufficiency, those already on corticosteroids or those who had received etomidate within a week prior to the cortisol sample collection were excluded from the study.
Approval to conduct the study was granted by the Research, Ethics and Publications Committee of the University of Limpopo (MEDUNSA Campus).

Statistics
Descriptive statistics are reported as mean ± SEM for normally distributed variables. Comparisons of categorical data were made using Fisher’s exact test. For all comparisons, differences were considered significant when p<0.05.

Results
152 patients were studied (mean age 37 ± 17.4). 41 patients met our criteria for the definition of adrenal insufficiency, giving an occurrence rate of 26.97% (CI: 19.91% - 34.03%). Table I shows the incidence of adrenal insufficiency in our population if we were to use other proposed literature criteria. There is a wide variation in the incidence depending on the cut off point chosen.

Sixty-four patients were in septic shock at the time of blood sampling. Only fifteen percent of these were confirmed to have adrenal insufficiency, compared to thirty-five percent of the cases that were not in septic shock. This difference was significant (p= 0.009). Patients with fluid-responsive shock had similar rates of adrenal failure to patients who required catecholamines for hemodynamic support (30% vs. 15.6%, p = 0.194).

The overall mortality was 24.3% (37/152). Only two of the deaths occurred in patients with confirmed adrenal failure. Forty-seven percent (30/64) of the cases with septic shock died. The mortality from all causes in the intensive care unit was significantly higher in patients without adrenal insufficiency (28.8% vs. 12.2%, p = 0.035). The death rate in patients with community-acquired sepsis was similar to that of patients with nosocomial sepsis (26.8% vs. 22.2%, p = 0.052).

There was also no statistically significant difference in the mortality rate between bacteraemic and blood-culture negative cases (25.71% vs. 24.35%, p = 1.000).

The mean APACHE II score for the group was 14 ± 6.79. Non-survivors had significantly higher APACHE II scores compared to the survivors (18.49 ± 6.76 vs. 13.41 ± 6.34, p <0.0001). Patients with ‘adequate’ adrenal function had higher illness severity scores when compared to those with adrenal failure (18.42 vs. 12.58 , p = 0.023).

The yield of the microbiologic investigations is shown in tables II and III. Gram- negative pathogens accounted for 54% of the culture-positive cases. Eleven percent of the episodes were poly-microbial.

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| TABLE I: Incidence of adrenal insufficiency in our study population according to previously published criteria. |
|-----------------|-----------------|-----------------|
| Author          | Defining cortisol level | Incidence     |
| Marik & Zaloga (2001) | <25µg/dl | 46%            |
| Annane et al (2005)  | <15µg/dl | 13%            |

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34% of the patients with gram-negative sepsis were in septic shock compared to 45.4% of the cases with gram-positive sepsis. This difference was not significant (p = 0.43).

Patients with bacteraemic sepsis were no more likely to have adrenal insufficiency compared to those without bacteremia (37.1% vs. 23.9%, p = 0.1332). There was also no statistically significant difference in the incidence of adrenal dysfunction between cases with gram-negative and those with gram-positive sepsis (p = 1.000). Patients with pulmonary sepsis had similar rates of adrenal failure as those with abdomino-perineal sepsis (25.9% vs. 18.8%, p = 0.3796).

The mean duration of ICU stay for the group was 7.99 ± 7.64. The length of stay in the intensive care unit did not differ significantly between the patients with and those without adrenal failure (9.38 vs.7.32, p = 0.072).

| TABLE III: Pathogens isolated |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Gram-negatives  | Gram-positives  | Fungi           | Mycobacteria    |
| Klebsiella species(18) | MSSA (7) | Candida albicans (2) | Mycobacterium tuberculosis (2) |
| Acinetobacter species(15) | MSSA (1) | Cryptococcus neoformans (11) | |
| Escherichia coli(7) | Enterococcus species (7) | Pneumocystis jirovecci (1) | |
| Pseudomonas species(7) | Streptococcus species (9) | | |
| Other Enterobacter species (4) | | | |
Vasopressor therapy was required in forty-two percent of the patients. Table IV shows the frequency and types of vasoactive agents used for hemodynamic support.

| VASOACTIVE AGENTS | NO. OF PATIENTS |
|--------------------|----------------|
| Adrenaline         | 26             |
| Dobutamine         | 12             |
| Dopamine           | 2              |
| Combination        | 24             |

**Discussion**

Based on this study adrenal insufficiency is probably not uncommon amongst our critically ill septic patients. A surprise finding was the relatively low occurrence rate of adrenal failure in patients with septic shock compared to other studies. The explanation for this seemingly contradictory finding may lie in the fact that most of the septic shock cases in this study had raised cortisol levels (mean 827.58 mmol/l). Plasma cortisol levels have been found to be higher in patients with septic shock and, especially those with a higher risk of dying. Overall the mortality rate in patients with impaired adrenal function in this study was low. This disorder is said to be associated with a high mortality, particularly if left untreated or when it is associated with septic shock. The death rate in patients with septic shock and adrenal failure in this study was low (0, 2%), but the small number of patients (10) suggests this to be a topic for further study. The prognostic value of secretory failure of the adrenal glands in patients with sepsis is still unclear. Some authors believe that the conflicting reports reflect a bimodal distribution of mortality in relationship to the random cortisol level during sepsis, with patients having extremely low cortisol levels (<25 µg/dl) and those who have very high levels (>45 µg/dl) having the highest mortality.

The diagnostic criteria for adrenal insufficiency remain unresolved. It is possible that the cut-off level for random cortisol used in our study is inappropriate, even though it has been used in other published reports. A recent study by Venkatesh et al, demonstrated that although random cortisol measurements and the low dose cosyntropin test reliably reflected the 24 hour mean cortisol in critical illness, they do not take into account the pulsatile nature of cortisol secretion, with potential for erroneous conclusion about adrenal function based on a single measurement. Of major concern is the marked difference in the incidence of adrenal failure in this study when the different criteria are used. Plasma cortisol determination is rapid and easy to perform (turn around time is less than half and hour).

Its advantage would be the ability of clinicians to introduce gluco-cortioid therapy early, and in appropriate patients. This would be provided a specific serum cortisol level has been validated for the diagnosis of adrenal failure. We are unaware of such a study. The use of ‘rapid’ shock reversal upon administration of exogenous steroids may not be a reliable means of evaluating adrenal insufficiency as corticosteroids have additional physiologic effects.

Our study suggests that gram-negative sepsis is still the more common in our intensive care unit patients. The occurrence rate of gram-negative sepsis is believed to have diminished over the years. The trend observed in many recent sepsis studies is that gram-positive bacteria have surpassed gram-negative pathogens as aetiological agents for sepsis. The importance of local surveillance cultures cannot be over-emphasized.

Epinephrine was the vasoactive agent most often used in this study. It has been recommended that its use in septic shock be limited because of its potential negative effects, with dopamine and/or nor-adrenaline being recommended for initial therapy. The use of vasoactive agents in this unit is not protocol-directed, and individual clinicians choose agents based on personal experience. Recommendations about the use of vasopressor agents in septic shock have been made difficult by the paucity of controlled trials and by the clinical reality that agents are frequently used in combination. The unit has no access to nor-epinephrine.

More than half of the infections were nosocomial in origin and accounted for half of the deaths observed in this study. The problem of hospital-acquired sepsis has become a cause for concern all over the world. It is believed to occur in 5-15% of hospital admissions, it is costly, and is estimated to account for a sizable number of deaths. These infections occur more frequently among patients in intensive care units. Accordingly, infection control measures are to be viewed as a priority and have to be integrated into the continuous process of improvement of quality of care.

The principles of infection control are simple and basic and easy to implement.

Some limitations of this study should be noted. Survival was restricted to survival at ICU discharge. Substantial long-term consequences have been reported for critically ill patients. As a result long-term survival and attainable quality of life have gained ground as outcome measures. Stimulation tests were not performed as this was an observational study. Whether these tests would have enhanced our study is a matter of conjecture as their validity remains questionable.

In summary, using a threshold value of <20 µg/dl for random plasma cortisol we were able to establish that adrenal failure is not uncommon in our critically ill septic patients. Consensus on the definition of adrenal failure is paramount to guide glucocorticoid therapy in critically ill patients.

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