Adrenocortical Insufficiency in Patients with Septic Shock: Incidence and Effect of Steroid Therapy

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Abstract

Introduction: Absolute or relative adrenocortical insufficiency (AI) is relatively common in septic shock patients. In some cases, septic shock refractory to IV fluids and vasopressors may show hemodynamic improvement after steroid therapy.

Objectives: To determine the incidence of AI in patients with septic shock, to clarify whether glucocorticoid supplementation is beneficial in patients with septic shock & its effect on mortality.

Methods: An observational prospective study was performed at Critical Care Department, Cairo University on 50 patients with septic shock who required vasopressor therapy after adequate fluid resuscitation without previous steroid intake. After measurement of baseline total cortisol, the patients were subjected to ACTH stimulation test (250 µg). Post-stimuli cortisol levels were drawn 60 minutes after. Adrenal dysfunction (AD) was defined as serum cortisol <20 µg/dl with Δ cortisol (60 min. post ACTH minus baseline) of ≤9 µg/dl. Functional hypoadrenalism (FH) was defined as serum cortisol <30 µg/dl or Δ cortisol ≤9 µg/dl. AI was defined as the presence of either AD or FH [1]. Patients with AI and patients who did not show any hemodynamic improvement after adequate fluid resuscitation and vasopressors therapy were given steroids. The steroid used was hydrocortisone 100mg/8hr till clinical improvement.

Results: Fifty pts; 27 males & 23 females with mean age 58.6±15.5 and mean APACHE II score 28.0±9.0. The commonest source of infection was multiple sources (32%) followed by abdominal infection (26%), infected wounds (24.0%), chest infection (16%) then urinary tract infection (12%). Hyperkalemia on admission was significantly higher in patients with AI (p=0.016). Statistically significant higher incidence of AI in pts with pre-existing liver disease (p=0.026). Steroids were given to 70% (35 patients) as follow: 38% (19 patients) with adrenal dysfunction, 24% (12 patients) with functional hypoadrenalism and 8% (4 patients) were given steroid empirically according to the guidelines of Surviving Sepsis Campaign.

Fifteen patients (43%) had initial hemodynamic improvement with no significant effect on mortality whether 10 days or overall mortality. Increased mortality in patients with AI (74.3%) vs those with no AI (53.6%), however it did not reach a statistically significant value, p=0.074. Overall mortality was 80% in all pts.


Key Words: Inflammation – Septic shock – Sepsis – Adrenal insufficiency – Outcome – Mortality.

Introduction

THE treatment of patients in septic shock with corticosteroids has been a controversial subject for many years [2]. The use of high doses of steroids became standard practice in the 1970s and 1980s [2-4]. Subsequently, in the late 1980s and 1990s, studies did not show an improved survival and some even demonstrated detrimental effects for patients treated with steroids [5-9]. At that time corticosteroids stopped being used for patients with sepsis and septic shock. More recently, the importance of inadequate adrenal corticosteroid production has been recognized with the increasing use of medications affecting adrenal cortex function and the decreased use of steroid treatment for sepsis [10]. In the late 1990s and early 2000s studies with lower doses of corticosteroids for longer periods demonstrated hemodynamic benefits [11-16]. Unfortunately, despite their potential benefits, corticosteroids also have adverse effects and the benefits and risks must be balanced in determining whether they should be used or not. Some of the serious adverse affects noted in patients with critically illness have included superinfections [2] and critical illness polyneuromyopathy [17,18].

Current guidelines for the use of steroids in septic shock recommend use of low-dose steroids...
for septic shock unresponsive to fluids and vasopressors. This recommendation was based on a study that showed a survival benefit in septic shock patients with no response to corticotropin stimulus who were treated with hydrocortisone and fludrocortisone \[13\]. The Hydrocortisone Therapy of Septic Shock (CORTICUS) study \[19\] was conducted to evaluate the efficacy and safety of low dose hydrocortisone in a broad population of septic shock patients.

**Aim of the work:**

The study aims to determine the incidence of AI in patients with septic shock, to clarify whether glucocorticoid supplementation is beneficial in patients with septic shock & its effect on mortality.

**Patients and Methods**

This study is an observational prospective study that was conducted at the Critical Care Department, Faculty of Medicine, Cairo University on 50 patients diagnosed as septic shock from the period of June 2009 to April 2010.

**Inclusion criteria:**

Patients with septic shock.

The definition of septic requires several criteria for diagnosis [20]:

- First, SIRS (systemic inflammatory response syndrome) must be met by finding at least any two of the following:
  
  Tachypnea (high respiratory rate) >20 breaths per minute, or on blood gas, a PCO \(_2\) less than 32mmHg signifying hyperventilation.

  White blood cell count either significantly low, <4000 cells/mm\(^3\) or elevated >12000 cells/mm\(^3\).

  Heart rate >90 beats per minute.

  Temperature: Fever >38.0\(^\circ\)C (100.4\(^\circ\)F) or hypothermia <36.0\(^\circ\)C (96.8\(^\circ\)F).

- Second, sepsis which requires evidence of infection, which may include positive blood culture, signs of pneumonia on chest X-ray, or other radiologic or laboratory evidence of infection.

- Third, signs of end-organ dysfunction are required such as renal failure, liver dysfunction, changes in mental status, or elevated serum lactate.

- Finally, septic shock is diagnosed if there is refractory hypotension to either IV fluids and vasopressors therapy (low blood pressure that does not respond to treatment). This signifies that intravenous fluid administration alone is insufficient to maintain a patient's blood pressure from becoming hypotensive.

**Exclusion criteria:**

- Patients with history of previous glucocorticoids intake.
- Known pre-existing adrenal disease.
- Adrenalectomy.

**Each patient was subjected to:**

**Complete physical examination searching for:**

- Source of infection.
- Signs of organ dysfunction.

**Vital signs monitoring including:**

- Blood pressure: Systolic, diastolic, mean arterial pressure & its response to steroid therapy.
- Heart rate.
- Core body temperature.
- Urine Output hourly.
- Central Venous Pressure: Optimized between 8-12cm H\(_2\)O.

**Routine laboratory work up:**

- Electrolytes: Na+, K+ levels.
- Arterial Blood Gases.
- Liver function tests.
- Kidney function tests.
- Coagulation profile.
- CBC with differential count.

- Culture & Sensitivity from the source of infection.
- Testing of adrenal function: The function of hypothalamic – pituitary – adrenal axis was assessed with short ACTH stimulation test which can be performed at any time of the day or night because it is not influenced by diurnal variations in cortisol secretion (which are often absent in critically ill patients). An initial blood sample is obtained for basal plasma cortisol level, and synthetic ACTH (250 \(\mu\)g) is injected intravenously. A post-ACTH plasma cortisol level is then obtained at 60 minutes after [21,22].

  The interpretation of the ACTH stimulation test using the basal cortisol level and the increment in cortisol at 60 minutes are used to evaluate adrenal function. In critically ill patients, adrenal dysfunction (AD) has been defined as the presence of random serum cortisol <20 \(\mu\)g/dl.

  An additional category, Functional Hypoadrenalism (FH) has been defined as the combina-
tion of random serum cortisol >20 µg/dl and Δ cortisol level of <9 µg/dl [23-28].

In the present study, AD was defined as serum cortisol <20 µg/dl plus Δ cortisol level after ACTH test of <9 µg/dl.

FH was defined by a cortisol level >20 µg/dl plus Δ cortisol level <9 µg/dl.

Adrenal Insufficiency (AI) was defined as the presence of either AD or FH. A positive hemodynamic response was defined as cessation of the need for vasopressor therapy to maintain MAP >65-70mmHg within 24 hours of the first hydrocortisone dose or within 24 hours of the ACTH stimulation test in patients not treated with hydrocortisone.

Grading for ICU mortality by APACHE II score:

Acute Physiology and Chronic Health Evaluation scoring system was applied for all patients to determine the severity of the underlying critical illness upon ICU admission within the first 24 hours [29].

The APACHE II scoring system was developed to provide an objective assessment of severity of illness in patients in the ICU.

The APACHE II score is made up of three components:
- Acute physiology score (APS): The largest component of the APACHE II score is derived from 12 clinical measurements that are obtained within 24 hour after admission to the ICU. The most abnormal measurement is selected to generate the APS component of the APACHE II score. If a variable has not been measured, it is assigned zero points.
- Age adjustment: Form one to six points is added for pts older than 44 years of age.
- Chronic health evaluation: An additional adjustment is made for patients with severe and chronic organ failure involving the heart, lungs, kidneys, liver, and immune system.

Statistical analysis: Data were coded and entered using the statistical package SPSS version 15.0. Data were summarized using mean and standard deviation for quantitative variables and number & percentage for qualitative variables. Comparisons between groups were done using chi-square test for qualitative variables and analysis of variants (ANOVA) & independent sample t-test for normally distributed quantitative variables while non parametrical Kruskal-Wallis test and Mann-Whitney test were used for quantitative variables which are not normally distributed. p-values less than or equal to 0.05 were considered as statistically significant.

Results

A- Descriptive:

- Age & sex distribution: The study included 50 patients: 27 males (54.0%) & 23 females (46.0%) with mean age 58.6±15.5 years.
- Co-morbidities: The most common associated co-morbidities are in order of frequency: Chronic liver disease (42%) followed by diabetes mellitus (38%), chronic renal diseases (36%), systemic hypertension (30%), cardiac disease (18) & pulmonary diseases (14%).

Table (1): Co-morbidities in the study group.

<table>
<thead>
<tr>
<th>Co-morbidities</th>
<th>Septic shock</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>19</td>
</tr>
<tr>
<td>Hypertension</td>
<td>15</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>7</td>
</tr>
<tr>
<td>Liver disease</td>
<td>21</td>
</tr>
<tr>
<td>Renal disease</td>
<td>18</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>9</td>
</tr>
<tr>
<td>Number of patients</td>
<td>50</td>
</tr>
</tbody>
</table>

- Glasgow coma scale: Mean GCS on admission was 9.1±4.0.
- APACHE II Score: Mean APACHE II score on admission was 28.0±9.0.
- Sources of sepsis: Multiple sources is the most common source of sepsis (32.0%) followed by abdominal infection (26.0%), infected wounds (24.0%), chest infection (16.0%) then UTI (2.0%).
- Post-operative sepsis: 40.0% (20 patients) had recent operation.
- Cultures: 48% (24 patients) had negative culture versus 52% (26 patients) with positive culture results including 40% (20 patients) with Gram +ve bacteria & 12% (6 patients) with Gram –ve bacteria.

The most common organisms are: Staphylococcus aureus & MRSA in 22.2%, Klebsiella in 15.8%, Acinetobacter in 12.6%, E.Coli in 7.9%, Pseudomonas in 6.3%, Candida Albicans was found in 6.3% & atypical bacteria in 19.0%.
• **Organ dysfunction:** 58% (29 patients) had multi-organ dysfunction. Renal failure was the most common single organ failing, it was found in 16% (8 patients), followed by liver failure in 6% (3 patients), coagulopathy in 4% and ARDS in 2%. 14% (7 patients) did not show any evidence of organ failure.

• **Ten day survival rate:** Ten day survival was 50.0% (25 patients).

• **Final outcome:** The mortality rate was 80% (40 patients) versus 20% survival (10 patients).

Table (2): Comparison between survivors and non survivors in the study group.

<table>
<thead>
<tr>
<th></th>
<th>Survivors</th>
<th>Non survivors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>10/50</td>
<td>40/50</td>
</tr>
<tr>
<td>Percentage</td>
<td>20%</td>
<td>80%</td>
</tr>
<tr>
<td>Age</td>
<td>58.8±11.2</td>
<td>58.3±24</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>23.2±14.8</td>
<td>28.6±16.4</td>
</tr>
<tr>
<td>Positive cultures</td>
<td>3 (30%)</td>
<td>23 (57.5%)</td>
</tr>
<tr>
<td>Organ dysfunction</td>
<td>Most of patients had renal failure</td>
<td>Multi-organ dysfunction</td>
</tr>
<tr>
<td>Source of sepsis</td>
<td>Multiple sources</td>
<td>Multiple sources &amp; abdomen</td>
</tr>
</tbody>
</table>

• Comparison between survivors & non survivors in septic shock group:

B- **Analytical:**

• **Adrenal insufficiency:** The mean cortisol level before ACTH stimulation test was 23.6±8.3 µg/dl versus 29.7±9.1 µg/dl after ACTH stimulation test.

Adrenocortical insufficiency (Adrenal Dysfunction or Functional Hypoadrenalism) was found in 62% (31 patients).

Regarding the types of adrenal insufficiency, adrenal dysfunction is more common than functional hypoadrenalism [38% (19 patients) versus 24% (12 patients) respectively].

• **Relation between adrenal insufficiency & mortality:** There was an increased mortality among patients with adrenocortical insufficiency; Mortality was 74.3% in patients with AI versus 53.6% in patients with no AI, however, it did not reach a statistically significant value, \( p \text{-value}=0.07 \).

• **Steroid therapy & improvement after therapy:** Steroids were given to 76% (35 pts) as follow: 38% (19 pts) with adrenal dysfunction, 24% (12 pts) with functional hypoadrenalism and 8% (4 pts) were given steroid empirically according to the guidelines of Surviving Sepsis Campaign. Steroid therapy was given in the form of hydrocortisone 100mg/8 hours. 43% (15 out of 35) showed hemodynamic improvement after steroid therapy.

• **Relation between steroid therapy & mortality:** There was lower 10-day mortality in the steroids treated group versus non steroids treated group (45% versus 75% respectively). There was no statistically significant difference between overall mortality in the steroids treated group versus non steroids treated group (84% versus 75% respectively, \( p=\text{NS} \)).

• **Relation between Potassium (K+) levels on admission & adrenocortical insufficiency:** In all patients, mean K+ level 4.7±1.4mEq/L.

Hyperkalemia (serum K+ level >5.5mEq/L) on admission was statistically higher in patients with adrenocortical insufficiency (\( p=0.02 \)).

• **Relation between cortisol level & albumin level:** There was a statistically significant lower total baseline & stimulated cortisol levels in patients who were hypoproteinemic (serum albumin level ≤2.5g/dl) as compared with patients with serum albumin level >2.5g/dl.

Table (3): Relation between cortisol level and serum albumin level.

<table>
<thead>
<tr>
<th></th>
<th>≤2.5g/dl</th>
<th>&gt;2.5g/dl</th>
<th>( p \text{-value} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline cortisol level</td>
<td>17.4±20.8</td>
<td>23.4±18.7</td>
<td>0.05</td>
</tr>
<tr>
<td>Cortisol level after ACTH stimulation</td>
<td>22.4±19.7</td>
<td>30.9±16.9</td>
<td>( p=\text{NS} )</td>
</tr>
</tbody>
</table>

• **Relation between adrenal insufficiency & liver disease:** There was a statistically significant higher incidence of adrenocortical insufficiency in patients with pre-existing liver disease; AI was found in 73.9% of patients with pre-existing liver disease versus 45.0% of patients with no previous liver disease (\( p=0.02 \)).

**Discussion**

Cortisol is a major stress response hormone that has metabolic, catabolic, anti-inflammatory and vasoactive properties on cardiac muscle and the peripheral vasculature \[30,31\].

Cortisol also has inotropic effects and modulates free water distribution within the vascular compartment \[32\].

In response to external or internal stress, total serum cortisol is increased, from 2 to 10 times the upper limit of normal, and there is a loss of diurnal variation during critical illness \[10,33-35\].

The failure to reach these levels in the stressed state has led to the diagnosis of adrenocortical insufficien-
The classic signs and symptoms of which are hypotension, hyponatremia, hyperkalemia, hypercalcemia, hypoglycemia, metabolic acidosis & eosinophilia [36].

Such classic findings are not distinguishing features, perhaps because of the combination of underlying disease and prior therapeutic intervention that obscured the clinical picture. In patients with sepsis or septic shock, diagnosis of adrenocortical insufficiency is based on measuring baseline & post ACTH stimulation cortisol levels. In our study, we aimed at early identification of adrenocortical insufficiency in septic shock patients and to clarify whether steroid therapy is beneficial and its effect on mortality.

In the present study, 63 patients were included with mean APACHE II score on admission 28.0 ± 9.0.

High values of APACHE II score predicts increased likelihood of mortality in the studied population.

Multiple sources of infection, intra-abdominal infections, infected surgical wounds & are the most common sources of sepsis in our study population followed by pulmonary infection which were the usual sources of infection in most of the studies [13,19].

Negative culture results were found in 48% of all patients, 40% showed gram +ve bacteria mainly staph aureus, 12% had gram –ve bacteria (eg. klebsiella, acinetobacter, pseudomonas) & 6.3% had fungal infection.

Salgado et al., [37] showed that 31.37% of 102 patients with septic shock yielded negative culture results, 67.6% yielded positive microbiological results with gram –ve bacilli, 33.3% with gram +ve cocci, fungi in 5.1% & bacteremia was detected in 21.6% of patients.

In Mouloudi et al. [38], a study included 16 patients, gram –ve bacteria was present in 87.5% (14 patients) while gram +ve bacteria was present in 18.75% (3 patients) & 2 patients only (12.5%) with negative culture results.

The higher incidence of negative culture results in our study is due to either prior antibiotic use before ICU admission or early sampling of culture.

The occurrence of gram-negative infection has decreased & gram positive and fungal infections have become more frequent [39].

Gram-positive organisms are better suited to invade host tissues and elicit, in general, a brisker phagocytic response than gram-negative organisms. The lack of endotoxin in the outer cell wall is compensated for by the presence of exposed peptidoglycan and a range of other toxic secreted products. It appears that cell wall components of gram-positive bacteria may signal via the same receptor as gram-negative endotoxin, although the type of signal and co-receptor may differ [40].

In our study, 58% of the patients had multi-organ dysfunction, 16% had renal failure, 6% had hepatic failure, 4% had coagulopathy & 2% had only ARDS.

However, Martin et al. [41] presented the probably most extensive data analysis including 750 million hospital records over 22 years identifying 10, 319, 418 cases of sepsis. The proportion of sepsis patients with any organ failure was 30.2%; organs that failed most frequently were the lungs (18%) and the kidneys (15%).

Regarding the incidence of adrenal insufficiency in our study, 62.0% of septic shock patients had AI based on basal cortisol level ≤20 µ/dl or Δ cortisol level post ACTH stimulation test ≤9 µ/dl.

These figures are in agreement with Mouloudi et al., 2008 [38] study in which adrenal insufficiency was diagnosed in 11 out 16 patients (68.7%) with septic shock by either baseline cortisol ≤10 µ/dl or Δ cortisol level ≤9 µ/dl.

Paul E. Marik et al., [42] studied 59 patients with septic shock. Thirty six patients (61%) had adrenal insufficiency when they used a baseline cortisol concentration of <25 µ/dl as the reference method.

In Annane et al. [13], 299 patients were included to study the effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. Incidence of adrenal insufficiency was 76.3% (229 of 299 patients).

However, our results do not match the study done by Emanuel P. Rivers et al., [1] which was done on 104 postoperative hypotensive patients who needed vasopressors, adrenal insufficiency was diagnosed in 34 patients (32.7%).

In Salgado et al. [37], adrenal insufficiency was identified in 23 patients (22.5%) considering either baseline cortisol ≤10 µ/dl or Δ cortisol level ≤9 µ/dl.
The results of both studies could be explained by the low cut-off value of basal cortisol level <10μg/dl by which adrenocortical insufficiency was defined and the fact that postoperative patients have elevated cortisol levels (stress response).

In critically ill patients there are a number of confounding factors that make interpretation of cortisol level difficult. Most importantly, the commercially available assays for serum cortisol determine the total (free plus protein-bound fractions) hormone concentrations. [43]

In healthy individuals more than 90% of circulating cortisol is bound to proteins [corticosteroid-binding globulin (CBG) & albumin], with less than 10% in the free, biologically active form. In critical illness CBG levels fall by approximately 50%, with marked inter-individual variation. Furthermore, as CBG binding sites becomes saturated the percentage of free cortisol increases. Hence, in critically ill patients the total cortisol may not reflect the biologically free (unbound) cortisol [43].

In critical illness, patients are highly stressed, multi-organ dysfunction and malnutrition may develop, and the concentrations of corticosteroid-binding globulin and albumin are commonly decreased. Therefore, measured serum total cortisol concentrations can be misleadingly lower than anticipated, resulting in the incorrect conclusion that adrenal function is impaired [44].

In our study, there was a significantly lower baseline cortisol level <2.5gm/dl (17.4±20.8 μg/dl & 22.4±19.7 μg/dl respectively) in comparison to patients with serum albumin level >2.5gm/dl (23.4±18.7 μg/dl & 30.9±16.9 μg/dl) with p=0.05.

The importance of serum albumin (a surrogate marker of CBG levels) when interpreting total serum cortisol concentrations is elegantly demonstrated by Salgado et al., 2006 [37] in a study included 102 patients with septic shock showed that total baseline & stimulated cortisol levels (15.5 μg/dl & 23.5 μg/dl respectively) were significantly lower in patients with serum albumin level <2.5gm/dl than in those with serum albumin level >2.5gm/dl (22.4 μg/dl & 40.3 μg/dl) with p=0.04.

Also, Hamrahian et al., 2004 [44] demonstrated that patients who were hypoproteinemic had significantly lower baseline cortisol level & stimulated levels (15.8±7.4 μg/dl & 23.4±9.5 μg/dl) as compared with patients who had serum albumin level >2.5gm/dl (22.6±8.9 μg/dl & 34.4±10.3 μg/dl) with p<0.001.

Sepsis and end-stage liver disease have a number of patho-physiologic mechanisms in common (e.g., endotoxemia, increased levels of pro-inflammatory mediators, and decreased levels of HDL), and it is, therefore, not surprising that adrenal insufficiency is common in patients with end-stage liver disease [45-47].

In our study, 73.9% of the patients with pre-existing liver disease had the biochemical diagnosis of adrenal insufficiency which is known as Hepatoadrenal syndrome.

These results are consistent with the results of Javier Fernandez et al., [48] which stated that relative adrenal insufficiency is a frequent feature in patients with liver cirrhosis & septic shock with prevalence of sixty-eight percent. They showed low baseline plasma cortisol concentration, low response to corticotropin or both.

Ming-Hung Tsai et al., [49] found that in critically ill patients with liver cirrhosis and severe sepsis, adrenal insufficiency occurred in 51.48% of patients with low baseline plasma cortisol concentration, low response to corticotropin or both.

Also, Arnaud Galbois, Marika Rudler et al., 2010 [50] conducted a study on 88 patients with liver cirrhosis (sepsis or septic shock patients were excluded) and found that 29 patients (33.0%) had adrenocortical insufficiency.

In our study, there was higher mortality rate (74.3%) among patients with adrenal insufficiency compared to (53.6%) mortality in patients with no adrenal insufficiency. However, it did not reach a statistically significant value.

These results were confirmed by the results of Sprung et al., 2008 [19] [CORTICUS study] which showed higher mortality 37.7% in patients with adrenal insufficiency compared to 28.7% mortality in patients with no adrenal insufficiency with no significant difference (p=0.69).

In our study, there was a statistically significant higher incidence of hyperkalemia (baseline serum K+ level >5.5mEq/L) in patients with adrenocortical insufficiency compared to patients with no adrenocortical insufficiency (p=0.016).

These results was confirmed by Michael Nagler et al., [51] who showed high incidence of severe hyperkalemia in cases of metastatic lung and breast...
cancer with bilateral adrenal metastasis which improved markedly after steroid therapy.

In our study, 15 patients (43%) out of 35 patients had initial hemodynamic improvement after steroid therapy (hydrocortisone 100mg/8 hours) for a period of 6.4±5.2 days, however, this did not affect overall mortality.

These figures are confirmed by the results of Emanuel P. Rivers et al., 2001 [1], a study included 104 patients, 46 patients (44.2%) received steroid therapy & 29 patients (27.8%) had weaned off of vasopressor therapy within 24 hours of the first hydrocortisone dose.

Paul E. Marik et al., [42] studied 59 patients with septic shock received hydrocortisone 100mg/8 hours. 22 patients (37%) had haemodynamic improvement after steroid therapy.

Sprung et al., [19] [CORTICUS study] had studied 499 patients with the diagnosis of septic shock. 251 patients received hydrocortisone therapy 50mg/6 hrs versus 248 patients received placebo. In the hydrocortisone group, shock was reversed more quickly than in the placebo group. However, there were more episodes of super-infection, including new sepsis and septic shock.

There was no statistically significant difference regarding reversal of shock after steroid therapy. The proportions of patients who underwent a reversal of shock were similar among all patients: 200 of 251 in the hydrocortisone group (79.7%) and 184 of 248 (74.2%) in the placebo group (p=0.18).

However, our results do not match with Mouloodi et al., 2008 [38] in which 12 patients (75%) out of 16 patients had improved haemodynamics with hydrocortisone therapy.

In Annane et al. [13], 299 patients with septic shock were divided into 2 groups. 149 patients given placebo & 151 patients given hydrocortisone 50mg/6 hrs plus fludrocortisone for 7 days with no tapering. Reversal of shock occurred more commonly (57%) in steroid-treated patients than placebo-treated patients (40%).

Regarding the effect of steroid therapy on mortality in our study, mortality was higher in steroid treated group compared to non treated group (84% versus 75% respectively, p=NS).

Several studies investigated the effect of steroid therapy on final outcome in critically ill patients with conflicting results:

In Bollaert et al. [11], 41 patients with septic shock were included & divided into 2 groups. 22 patients were given hydrocortisone 100mg/8 hrs for 5 days then tapering in the 6th day. The mortality rate was 32% (7 out of 22 patients) in steroid treated group versus 63% in placebo group. The main causes of death were progression of multi-organ failure & new episodes of shock after reversal of first shock state.

In Briegel et al. [12], 40 patients with septic shock given 100 mg bolus then 0.18mg/ kg/day till shock reversal showed 25% mortality (10 out of 40 patients) died from refractory hypotension, pulmonary embolism & second episode of septic shock occurred 3, 30, 50 days after reversal of first shock state.

Chawla et al., [52] studied 44 patients with septic shock divided to 2 groups. 21 patients given placebo & 23 patients were given hydrocortisone 100mg/8 hrs for 3 days then tapering in the 4th day. Mortality rate was 39.13% (9 out of 23) in steroid treated group versus 47.6% (10 out of 21) in placebo group with no significant difference (p>0.05).

In Emanuel P. Rivers et al. [1], mortality was significantly lower in the glucocorticoids-treated group (21%) than in the untreated group (45%), p<0.01.

Annane et al. [13], 299 patients with septic shock divided into 2 groups. 149 patients given placebo & 151 patients given hydrocortisone 50mg/6 hrs plus fludrocortisone for 7 days with no tapering.

In 114 patients with adrenal insufficiency, mortality was lower [53% (60 patients)] in patients treated with steroids versus 63% in placebo group.

Meduri et al. [53], studied 91 patients with early severe ARDS and divided them into 2 groups. 28 patients given placebo & 63 patients given methylprednisolone 1mg/kg/day infusion for 21 days maximally.

Mortality was 23.8% (15 patients) in steroid treated group & 42.8% (12 patients) in placebo group.

The above studies showed decreased mortality with steroid therapy which was opposed by the following studies:

In Confalonieri et al. [54], 46 patients with severe sepsis/pneumonia were classified into 2 groups. 23 patients given placebo & 23 patients...
given hydrocortisone 200mg bolus then 10mg/hour for 7 days.

At 8th day, 9 patients of the hydrocortisone treated group developed delayed septic shock from which 2 patients died (22.2%).

In Oppert et al. [15], 41 patients with septic shock were given hydrocortisone 100mg bolus then 0.18mg/kg/hr till shock reversal showed 68.2% mortality.

In Sprung et al. [19], 499 patients with septic shock were divided into 2 groups; 248 patients received placebo & 251 patients given hydrocortisone 50mg/6 hrs for 5 days. It was found that there were no differences in 28-day mortality in patients treated with steroids (34%) versus 32% in placebo group.

In our study, 10-day mortality was 50% and Final outcome showed 80% mortality. The higher mortality rate in our study could be attributed to high APACHE II score levels on admission, multi-organ dysfunction, pre-existing diseases, complications of steroid therapy (e.g; superinfections, impaired wound healing, myopathy) & recurrence of shock after initial improvement.

This is close to the study by Muzaffar Maqbool et al., [55] which included 30 patients with septic shock, the 28-day mortality rate was 60% (18 patients).

On the other hand, several studies showed less mortality:

Emanuel P. Rivers et al., 2001 [1], overall mortality was 40% (42 of 104 patients with post-operative hypotensive patients).

Paul E Marik et al., [42] studied 59 patients with septic shock with overall mortality 28 patients (47%).

In Salgado et al. [37], overall mortality was 45.1 % of 102 patients with septic shock.

In Mouloudi et al. [38], mortality was 43.7% (7 out of 16 patients with septic shock).

Several factors have been suspected to be associated with mortality in cases of severe sepsis and septic shock [56-58]. The main prognostic factors reported are age, severity of the patient’s underlying disease, number of organ system dysfunctions, severity of illness scores, hypothermia, neutropenia, thrombocytopenia, lactic acidosis, multisource of infection, positive blood culture, type of infecting organism, blood concentrations of endotoxin, and cytokines.

In the present study, we found three factors significantly high associated with increased mortality: Higher APACHE II score values, more patients with positive culture results & higher incidence of multi-organ dysfunction.

References


Adrenocortical Insufficiency in Patients with Septic Shock, Incidence


