Original Article

Adrenal Insufficiency in Patients with Liver Cirrhosis and Severe Sepsis: Effect on Survival after Treatment with Hydrocortisone

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ABSTRACT

Background & Aims: Bacterial infections are common complications in patients with liver cirrhosis and are associated with a high mortality. Standard treatment outcome is limited. The aim of this study was to determine whether or not early assessment of adrenal functions and treatment with hydrocortisone in patients with relative adrenal insufficiency with severe sepsis could improve survival.

Methods: Patients with liver cirrhosis and severe sepsis were randomly assigned to receive either early assessment of adrenal functions within 24 hours of admission (Group 1) or no early assessment (Group 2). Standard treatment of severe sepsis was given in both groups. Low dose hydrocortisone (50 mg IV every 6 hour) was prescribed in patients with relative adrenal insufficiency. The study end point was at day-28 of hospitalization.

Results: Thirty-nine patients were enrolled and were randomized in two groups. There were 20 patients in group 1 and 19 patients in group 2. The occurrence of relative adrenal insufficiency was 20% (4 of 20 patients). Ten patients in Group 1 (50%) and 8 patients in Group 2 (42%) died while under treatment. Four patients in Group 1 were treated with hydrocortisone. Hospital survival rates at days-28 were 50% and 57.9% in Group 1 and Group 2, respectively ($p = 0.62$). Complications of cirrhosis; refractory shock, hepatorenal syndrome, gastrointestinal bleeding, bacterial resistance, fungal infection, in both groups were comparable and without statistical significance.

Conclusion: In this study, the useful of adrenal assessment and hydrocortisone treatment did not increase survival rate. Further studies with larger sample size and proper tests for adrenal assessment are needed for confirmation.

Key words : Adrenal insufficiency, cirrhosis, sepsis, hydrocortisone

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Bacterial infection is a frequent complication and an important cause of death in patients with advanced liver cirrhosis[1-3], the infection related mortality rate being approximately 30%. Prognosis of patients with cirrhosis admitted with septic shock is even worse, the hospital mortality ranging from 60% to 100%[4-6]. Survival of cirrhotic patients with septic shock has not improved greatly during the past decade despite advances in antibiotic treatment and general supportive measures.

During the last few years, several studies have shown that septic shock is frequently associated with relative adrenal insufficiency, a condition characterized by an inadequate production of cortisol with respect to the peripheral demands. It also has been reported that patients with septic shock and relative adrenal insufficiency show resistance to vasoconstrictor drugs, a higher incidence of refractory shock and very high hospital mortality rate[7]. Various clinical trials and meta-analyses[8-11] show that the administration of low doses of hydrocortisone for several days in general patients with septic shock improve shock reversal and survival rates.

Standard treatment of septic shock consists of adequate fluid resuscitation, vasopressor drugs to maintain arterial pressure after appropriate fluid resuscitation in cases with persistent hemodynamic instability, as well as other supportive measures. Hydrocortisone therapy in cirrhotic patients with severe sepsis is controversial[12]. Only one prospective study[13] reported a beneficial effect of hydrocortisone in improving survival of cirrhotic patients septic shock. We decided to introduce the assessment of adrenal function in the management of all patients with liver cirrhosis admitted to our medical department, and to treat those patients with relative adrenal insufficiency with low dose hydrocortisone. The aim was to compare the clinical course and hospital mortality between the new approach and the standard treatment groups.

METHODS

Patients

Thirty-nine consecutive patients with liver cirrhosis and severe sepsis admitted at the Department of Medicine, Vajira Hospital, between November 2007 and December 2008 were evaluated for inclusion in the study. All patients or their relatives gave written informed consent to participate in the study. Inclusion criteria were: (1) liver cirrhosis, diagnosed by liver biopsy, clinical, biochemical, ultrasonographic and/or endoscopic findings; (2) severe sepsis, diagnosed clinically by the presence of data compatible with systemic inflammatory response syndrome with signs of organ failure, such as oliguria, acute creatinine elevation, lactic acidosis, coagulopathy, hypoxemia, hypotension, and acute alteration of consciousness. Two or more of the following criteria were required to diagnose the presence of systemic inflammatory response syndrome; temperature greater than 38 ˚C or less than 36 ˚C, heart rate greater than 90 beats/min, tachypnea greater than 20 breaths/min, white cell count greater than 12×10^9 /L or less than 4×10^9/L or more than 10% of immature neutrophils; (3) age 18 to 75 years. Exclusion criteria included: (1) human immunodeficiency virus infection, (2) patients with cirrhosis after organ transplantation, (3) advanced hepatocellular carcinoma, (4) history of steroid treatment in the previous 6 months and absence of drugs inhibiting steroidgenesis, and (5) active bleeding. This study was approved by the Hospital Ethics Committee.

Study design

This prospective, randomized, controlled study was conducted at a single academic centre. Candidate patients entering the study were randomized into two groups, Group 1 and Group 2. Patient assessment and treatment of septic shock was uniform in both groups, except for the evaluation of adrenal function and treatment with hydrocortisone in Group 1 patients with relative adrenal insufficiency. A central intravenous line and a urinary catheter were inserted in every case for the diagnosis and early management of severe sepsis. Ascitic fluid leukocyte concentration, fresh urine sediment, blood culture, ascitic fluid culture, and urine culture, and chest X-ray were obtained. Bronchial samples were obtained and cultured in case of pneumonia. Physical examination, chest radiographs, and standard laboratory measurements were repeated after admission in all cases. Patients were treated according to a standard protocol that included fluid resuscitation with colloids to maintain a right atrial pressure of approximately 14 mmHg with dopamine (1-20 μg/kg/min) or norepinephrine (0.05-4 μg/kg/min) so as to achieve a mean arterial pressure above 70 mmHg. Patients with spontaneous bacterial peritonitis additionally received intravenous albumin (1.5 g/kg at diagnosis, and 1 g/kg on day 3). Albumin was also prescribed

in cases with serum albumin below 2.0 g/dL (dosages adjusted to increase albumin level to more than 2.5 g/dL). Antibiotics were administered in both groups according to a previously defined local protocol on the treatment of bacterial infections in cirrhosis. Patients with severe renal failure were treated with continuous renal replacement, and those with severe respiratory failure were mechanically ventilated.

The severity of hepatic failure was estimated with the Child-Pugh and the Model for End-stage Liver Disease (MELD) scores. The severity of illness was assessed with the SOFA (Sequential Organ Failure Assessment). Renal failure was diagnosed when serum creatinine concentration was greater than 1.5 mg/dL. Type 1 hepatorenal syndrome was defined according to the International Ascites Club 2007. The diagnostic criteria for spontaneous bacterial peritonitis, pneumonia, urinary tract infections, and other bacterial infections have been previously reported. Refractory shock was defined as a state of shock not responding to therapy with volume expansion and high doses of vasopressors. Acute respiratory distress syndrome was considered when patients developed acutely bilateral chest radiographic infiltrates and hypoxemia in the absence of signs of cardiac dysfunction.

In Group 1 patients, a Controsyn Test was performed within the first 24 hours of admission. Synthetic adrenocorticotrophic hormone (250 μg, Controsyn®, Zuellig pharma) was given intravenously. Blood sample to measure plasma cortisol levels were obtained before and 60 minutes after Controsyn administration. Relative adrenal insufficiency was diagnosed when one of the following two criteria was met: (1) baseline cortisol concentration less than 15 μg/dL; (2) increase in plasma cortisol after Controsyn administration lower than 9 μg/dL in patients with baseline cortisol concentration below 35 μg/dL. Patients with relative adrenal insufficiency received 50 mg intravenous hydrocortisone every 6 hour. Treatment was gradually discontinued (reduction of 50 mg/d) when patients did not require vasopressor drugs to maintain arterial pressure.

Study end points

The primary end point was hospital survival at day-28. The new modality approach with assessment of adrenal function and treatment with hydrocortisone in patients with cirrhosis and severe sepsis was compared to the standard treatment.

Statistical analysis

Continuous variables were reported as mean ± SD or median and compared by the student *t*-test or by the Mann-Whitney-Wilcoxon test when indicated. Discontinuous variables were compared by the Chi-square test. Probability curves were obtained by Kaplan Meier method. Calculations were performed with the SPSS Statistical Package (SPSS version 11.5). Differences were considered significant at $p < 0.05$.

RESULTS

Thirty-nine patients were enrolled in this study, 29 in Group 1 and 19 in Group 2. The mean patient age was 58.7 ± 12.0 in Group1 and 53.2 ± 11.0 in Group 2. There were no significant differences in clinical baseline characteristics, demographic, clinical, laboratory data, and the course of septic shock between the two groups (Table 1). 8 patients (40%) in Group 1 and 8 patients (39%) in Group 2, the bacteria responsible for septic shock were identified. The most frequent bacteria isolated in this study were gram-negative bacilli (56% culture positive). No significant differences were found between the two groups with regard to the degree of hepatic failure as estimated by the Child-Pugh and the Model for End-Stage Liver Disease scores, and the severity of illness as estimated by the SOFA score. Thirteen patients (65%) from Group 1 and 9 patients (47.4%) from Group 2 had respiratory failure. Seven patients in Group 1 (35%) and five patients in Group 2 (26%) were diabetics. Acute renal failure developed in 17 patients (85%) in Group 1 and in 12 patients (63.2%) in Group 2. Recovery from renal failure was noted in 8 patients (47%) in Group 1 and in 6 patients (50%) in Group 2.

Incidence of relative adrenal insufficiency

Adrenal insufficiency tests were carried out 20 patients in Group 1, 4 of 20 (20%) were tested positive. Cirrhosis status of the four patients was Child A: 1 patient, Child B: 2 patients, Child C: 1 patient. The etiology of shock was spontaneous bacterial peritonitis (1 case), urinary tract infection (1 case), pneumonia (1 case) and unknown (1 case). Adrenal insufficiency in spontaneous bacterial peritonitis was noted in 1 of 6 patients (16.6%).

Clinical course

Septic shock was identified in 11 patients (58%)

Table 1. Clinical baseline characteristics at admission in Group 1 and in Group 2.

	Group 1 (N = 20)	Group 2 (N = 19)
Age (years)	58.7 ± 12.0	53.2 ± 11.0
Male sex (%)	11 (55%)	14 (73.7%)
Alcoholic cirrhosis (%)	14 (70%)	18 (94.7%)
Hepatitis C (%)	2 (10%)	2 (10.5%)
Hepatitis B (%)	6 (30%)	11 (57.9%)
Temperature (˚C)	38.0 ± 0.9	38.3 ± 0.8
Mean arterial pressure (mmHg)	75.0 ± 20.0	81.0 ± 19.0
Heart rate (beats/min)	112 ± 14	99 ± 14
Hematocrit (%)	29.0 ± 5.5	28.0 ± 6.7
Leukocyte count ($\times 10^9$/L)*	7850	7200
Platelet count ($\times 10^9$/L)*	815000	113000
Aspartate aminotransferasen level (IU/L)*	77	89
Alanine aminotransferase levels (IU/L)*	34	42
Serum bilirubin (mg/dL)	5.9 ± 5.3	5.6 ± 3.8
Serum albumin (g/dL)	2.3 ± 0.5	2.2 ± 0.5
Prothrombin index (%)	18.6 ± 6.9	15.8 ± 6.9
Serum creatinine (mg/dL)	2.0 ± 0.5	1.84 ± 0.9
Renal failure (%)	17 (85%)	12 (63.2%)
Serum sodium (mEq/L)	134 ± 4.8	135 ± 7.8
Ascites (%)	18 (90%)	15 (78.9%)
SBP (%)	5 (25%)	3 (15.8%)
Hepatic encephalopathy (%)	8 (40%)	11 (57.9%)
Child Pugh A/B/C (%)	2 (10%), 5 (25%), 13 (65%)	0 (0%), 8 (42%), 11 (57%)
MELD (score)	22.9 ± 8.4	20.6 ± 6.7
SOFA (score)	11 ± 2	10 ± 2.5
Etiology of septic shock (%)		
Pneumonia	5 (25%)	5 (26%)
Spontaneous bacterial peritonitis	2 (10%)	2 (10%)
Urinary tract infection	2 (10%)	3 (15.8%)
Gastrointestinal tract infection	6 (30%)	4 (21%)
Not indentify	5 (25%)	5 (26%)
Mechanical ventilation (%)	12 (60%)	10 (52.6%)
Treatment with dopamine / norepinephrine (%)	7 (35%)	5 (26%)

*Report as median value

in Group 1 and 7 patients (36.8%) in Group 2 (p = 0.26). One patient in each group (5.0% and 5.3%) developed refractory shock. Infection with resistant bacteria was seen in 2 patients (10.5%) in Group 2 and none in Group 1 (p = 0.23). Gastrointestinal hemorrhage, 3 patients (15%) in Group 1 and 5 patients (26.3%) in Group 2 (p = 0.45). One patient in Group 2 developed fungal infection. Hepatorenal syndrome was diagnosed in 1 patient (5%) in Group 1 and in 3 patients (15%) in Group 2 (p = 0.34). There were no significant differences in the clinical course between the two groups.

Survival

Ten patients (50%) from Group 1 and eight patients (42%) from Group 2 died during the course of treatment. Common complications are listed in Table 2.

Four patients in Group 1 were treated with hydrocortisone, their ages were 40, 70, 76 and 79. Child

Table 2. Complications of cirrhosis and severe sepsis in Group1 and Group 2.

	Group 1 (N = 20)	Group 2 (N = 19)	*p*-value
Refractory shock (%)	1 (5%)	1 (5.3%)	0.97
Hepatorenal syndrome (%)	1 (5%)	3 (15.8%)	0.34
Gastrointestinal bleeding non-variceal (%)	3 (15%)	5 (26.3%)	0.45
Acute renal failure	17 (85%)	12 (63.2%)	0.12
Liver failure	7 (35%)	4 (21%)	0.33
Bacterial resistance	0	2 (10.5%)	0.23
Fungal infection	0	1 (5.3%)	0.48

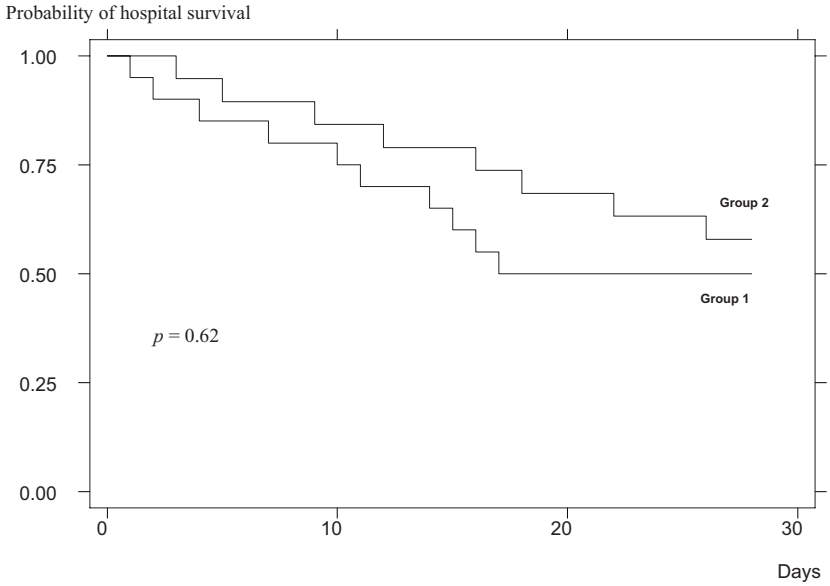

Figure 1. Probability of hospital survival curve at day-28 in Group 1 and Group 2 by Kaplan-Meier method.

Pugh score was A = 1, B = 2 and C = 1 patients. Two patients were diabetics. Liver failure and respiratory failure needing ventilatory support developed in 1 patient. The etiology of shock in the latter patient was urinary tract infection. Renal failure developed in 2 patients, one with HRS and the other with pre-renal failure. Gram-positive bacterial infections were identified in 2 patients. All patients with relative adrenal insufficiency who were treated with hydrocortisone survived, but no statistical difference in survival between the two groups was noted (Figure 1).

DISCUSSION

Adequate adrenal function is fundamental to survival in the face of a critical illness. Cortisol is vital in the host adaptation to stress. It is essential to maintain the normal vascular tone, endothelial integrity, vascular permeability, cardiac response to renin-angiotensin, the sympathetic nervous systems and the distribution of total body water within the vascular compartment. Consequently, the failure of an appropriate adrenal response in the setting of a critical illness, an abnormality known as relative or functional adrenal insufficiency, may have important clinical consequences. Such patients still secrete cortisol, and corticotrophin in the early phases of critical illness, but less than expected during acute stress[7-9].

The mechanisms of adrenal insufficiency in septic shock are not well established. Normally in severe sepsis, activation of the hypothalamic pituitary adrenal axis is an important feature in host adaptation to other acute illness. Activation of the system is initiated by the action of cytokines on the hypothalamus promoting the release of corticotrophin releasing hormone, stimulating corticotrophin secretion by the pi-

tuitary gland, which in turn increases cortisol secretion by the adrenal glands. The level of cortisol binding protein decreases rapidly during severe sepsis, leading to an increase of free circulating cortisol, an active component. During an acute illness, the negative feedback of cortisol on the release of corticotrophin releasing hormone and corticotrophin is depressed, and keeps a sustained activation of the hypothalamic pituitary adrenal axis. Finally, cytokines increase the affinity of cortisol to glucocorticoid receptors. Consequently, during severe sepsis, in well compensated adaptation response to optimize the effect, cortisol level in the circulation and in the tissue is increased[7,15].

In cirrhosis, there may be a reduction in adrenal blood flow. Very high levels of inflammatory cytokines directly inhibit adrenal cortisol synthesis, and the cytokine response to endotoxin is vastly increased, thus blood perfusion to extrasplanchnic organs is generally reduced. Furthermore, cholesterol, which is a precursor for cortisol synthesis, is lowered. As indicated above, cirrhotic patients may present with relative adrenal insufficiency prior to an infection. The diagnosis of relative adrenal insufficiency cannot be mode on clinical grounds. It is frequently associated with a study of shock refractory of vasopressor drugs, multiple organ failure, and death. Thus early diagnosis is crucial. The diagnosis of relative adrenal insufficiency in critically ill patients relies on the measurement of plasma cortisol levels before and after adrenal stimulation with synthetic corticotrophin. There is evidence to support the use of low dose of corticosteroids (hydrocortisone 50 mg every 6 hour) in septic shock, especially if there is biochemical evidence of relative adrenal insufficiency. Several randomized controlled trials in patients with septic shock have shown improvements in hemodynamics, reduction in the need of vasopressors, and a significant decrease in mortality[7-9].

Four studies have recently assessed adrenal functions in patients with liver cirrhosis and severe sepsis or septic shock, and have suggested that there is a relative adrenal insufficiency in this setting. The first study by Harry *et al*[14] was mode in 45 patients with fulminant hepatic failure. Sixty-two percent of cases showed relative adrenal insufficiency, which was associated with a higher incidence of cardiovascular instability requiring vasopressors support, a more severe illness, and a higher rate of hospital mortality or liver transplantation. The second was retrospective comparative study, also by Harry *et al*[12], on the use of stress doses of hydrocortisone in patients with liver disease and septic shock, was conducted in 40 patients with hypotension requiring vasopressors support. Twenty patients were treated with continuous infusion of 300 mg/day of hydrocortisone for 4 to 5 days, and the twenty patients were not receiving hydrocortisone admitted during the same period. Adrenal function was assessed in patients receiving hydrocortisone. Baseline cortisol and response to corticotrophin were below normal in 30% and 70% of patients respectively. Hydrocortisone reduced norepinephrine requirments. No difference was seen in hospital survival. The third study by Tsai *et al*[7] was performed in 101 patients with cirrhosis and severe sepsis requiring intensive monitoring or treatment. Based on the same criteria as in the present study, 50 of Tsai's 101 patients had septic shock. Adrenal insufficiency was diagnosed in 52 % of the patients and was significantly associated with septic shock, disease severity, renal failure, and hospital mortality. This latter study therefore suggested that the relative adrenal insufficiency may develop in patients with acute or chronic liver failure, and is a frequent event in patients with cirrhosis in septic shock. The fourth study was by Fernandez *et al*[13], prospectively evaluating the effects of steroids on shock resolution and hospital survival in a series of 25 consecutive patients with cirrhosis and septic shock. The results were compared to those obtained from a later group of 50 consecutive patients with cirrhosis and septic shock in whom adrenal function was not investigated and steroid treatment was not prescribed. The occurrence of adrenal insufficiency was 68%. Adrenal dysfunction was frequent in patients with advanced liver cirrhosis (Child C: 76% vs. Child B: 25%). Resolution of septic shock (96% vs. 58%), and hospital survival (64% vs. 32%, $p = 0.003$) were compared. The main causes of death in the treatment group were hepatorenal syndrome and liver failure. In contrast, refractory shock led to most of the deaths in the non-treatment group.

In our study, we assessed adrenal function and the effect of supplemental treatment with low dose hydrocortisone in patients with cirrhosis and severe sepsis. We performed a prospective randomized therapeutic controlled trial, which differed from Fernandez *et al*[3] study in one prospective group and a retrospective control group. We decided to assess adrenal function and treatment of evidently relative adrenal insufficiency in patients in Group 1 compared to Group 2 without adrenal function investigation. We wanted to

gain more information on adrenal dysfunction in our patients and the clinical course in both patient groups. The primary outcome in our study was hospital survival at day-28.

There were no statistically significant differences between the two groups regarding the demographic data, patients baseline clinical characteristics at admission, laboratory data, hospital course, complications of cirrhosis and severe sepsis, etiology of shock, organism, bacterial resistance, and fungal infection. Our results do not suggest that relative adrenal insufficiency is frequent in patients with cirrhosis and severe sepsis, as indicated from Fernandez *et al* study[13]. We found that only 20% of our patients had adrenal insufficiency (4 of 20 patients). The survival data in both groups were not statistically different (50% vs. 58%), although interesting by all patients with relative adrenal insufficiency treated with hydrocortisone survived. However, we could not evaluate more precisely the benefit of treatment with hydrocortisone on survival. The limitation in our study was the small number of patients. Other factors that could influence the results were ethnicity, geographic and environmental variation, severity of infection as required the inclusion criteria (severe sepsis and septic shock), diagnostic test criteria. Additionally, the definition of relative adrenal insufficiency in Asian population may differ from in Western. The 250 μg ACTH stimulation test induces supraphysiologic ACTH concentration and the 1 μg ACTH stimulation has been suggested as being more sensitive for diagnosis[15]. Further studies on adrenal function in patients with cirrhosis and severe sepsis and the effect of hydrocortisone treatment on survival are needed.

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