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Original Article

Early predictors of acute kidney injury in patients with cirrhosis and bacterial infection: urinary neutrophil gelatinase-associated lipocalin and cardiac output as reliable tools

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Abstract

Background: Hemodynamic abnormalities and acute kidney injury (AKI) are often present in infected cirrhotic patients. Hence, an early diagnosis of AKI is necessary, which might require the validation of new predictors as the determinations of urinary neutrophil gelatinase-associated lipocalin (uNGAL) and cardiac output.
Methods: We evaluated 18 infected cirrhotic patients subdivided into two groups at admission (0 hours). In Group I, we collected urine samples at 0 hours, 6 hours, 24 hours, and 48 hours for uNGAL and fractional excretion of sodium determinations. In Group II, we measured cardiac output using echocardiography.
Results: The age of patients was 55.0 ± 1.9 years, and 11 patients were males. The Model for End-Stage Liver Disease score was 21 ± 1, whereas the Child–Pugh score was C in 11 patients and B in 7 patients. Both patients in Group I and Group II showed similar baseline characteristics. In Group I, we diagnosed AKI in 5 of 9 patients, and the mean time to this diagnosis by measuring serum creatinine was 5.4 days. Patients with AKI showed higher uNGAL levels than those without AKI from 6 hours to 48 hours. The best accuracy using the cutoff values of 68 ng uNGAL/mg creatinine was achieved at 48 hours when we distinguished patients with and without AKI in all cases. In Group II, we diagnosed AKI in 4 of 9 patients, and cardiac output was significantly higher in patients who developed AKI at 0 hours.
Conclusion: Both uNGAL and cardiac output determinations allow the prediction of AKI in infected cirrhotic patients earlier than increments in serum creatinine.

Introduction

Bacterial infections are responsible for 30–50% of hospital admissions among patients with cirrhosis [1]. Infection sites include the peritoneum, urinary tract, lungs, and dermis [2]. Patients with cirrhosis and bacterial infection have a high incidence of acute kidney injury (AKI), which occurs in about one-third of these patients. The mortality rate by bacterial-induced infection AKI ranges from 15% to 78% depending on the site of infection and stage of cirrhosis [1].

Early recognition and treatment of such a severe complication in cirrhotic patients is correlated with better clinical outcomes [3]. In the past three decades, treatment with suitable antibiotics and large-volume albumin infusion in the

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first 6 hours from diagnosis of infections has reduced mortality rates from 80% to 20%. In addition, AKI development also reduced by almost 70% in these patients [3,4]. However, the benefit of such a treatment may be restricted to high-risk patients with serum creatinine (SCr) >1 mg/dL and/or serum bilirubin >4 mg/dL [5–7].

Although SCr and fractional excretion of sodium (FENa) have been used to identify patients with AKI, there is great concern about their limitations. Besides being a marker of renal function rather than kidney injury, SCr may be underestimated in cirrhotic patients because of their hypervolemic state, low muscular mass, and decreased hepatic production of creatinine [8]. Furthermore, SCr may take up to 2 days to increase after kidney injury. For these reasons, using SCr to identify high-risk patients among those with cirrhosis and bacterial infection may overlook a significant number of patients.

Urinary neutrophil gelatinase-associated lipocalin (uNGAL) has been used as a better predictor of AKI than SCr and FENa [9]. NGAL is a 22-kDa peptide expressed by activated neutrophils and kidney tubular injured cells. It is eliminated in urine, and its dosage may rise 6–48 hours before SCr in patients with AKI.

Another potential marker of AKI development in patients with cirrhosis is cardiac output. A previous study demonstrated that low cardiac output in cirrhotic individuals in the outpatient setting predicted AKI development in the subsequent year [10]. In addition, Ruiz-del-Arbol et al [11] also reported similar findings in patients admitted to hospital with tense ascites without bacterial infections. However, no studies to date have correlated cardiac output at admission and AKI development during bacterial infection in cirrhosis.

Thus, we hypothesized that uNGAL and cardiac output may be early predictors of AKI in patients with cirrhosis and bacterial infection.

Methods

Study patients

We conducted this study at the Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, which is a tertiary care hospital in Sao Paulo, Brazil, from November 2011 to June 2012. We evaluated 18 consecutive patients in whom cirrhosis and bacterial infection were present at admission. We diagnosed cirrhosis by liver biopsy or a combination of clinical, laboratory, radiological, and endoscopic data, and we defined bacterial infection according to the International Sepsis Definitions Conference 2001 [12]. We excluded patients with severe comorbidities, septic shock, chronic kidney disease, use of nephrotoxic drugs, hemodialysis treatment, or pre-existing liver transplantation.

All patients had clinical and laboratory data collected at admission (0 hours) to evaluate hepatic and renal functions at that time. Moreover, we measured SCr daily during hospital stay to AKI diagnosis. We defined AKI as the conventional criteria used in cirrhotic patients (i.e., a rise in SCr of at least 50% from baseline to a final value above 1.5 mg/dL) [13].

In our institution, the treatments of patients with cirrhosis and AKI are as follows: (1) patients with suspected prerenal azotemia receive resuscitation volume with crystalloids or albumin according to the physician's decision and (2) patients with suspected hepatorenal syndrome receive albumin 1 g/kg/d for 2 days and, if renal function does not improve, we prescribe terlipressin in combination with albumin infusion.

We divided the patients into two groups: those for uNGAL measurements (Group I) and those for cardiac output study (Group II).

In Group I, we collected urine samples at 0 hours, 6 hours, 24 hours, and 48 hours for NGAL and FENa determinations. We measured uNGAL in duplicate using an enzyme-linked immunosorbant assay kit (NGAL ELISA human kit 036, BioPorto Diagnostics, Gentoft, Denmark), and we used the cutoff values of uNGAL of 68 ng and 130 ng NGAL/mg creatinine in agreement with previous studies [14,15]. We also quantified urinary and plasma sodium for FENa determinations using flame photometry (model FC 280, CELM, São Paulo, SP, Brazil).

In Group II, we measured outflow tract area of left ventricle, velocity-time integral, and heart rate by echocardiography at admission, and we calculated cardiac output using the formula:

$$\text{cardiac output} = \text{left ventricle outflow tract area} \times \text{velocity time integral} \times \text{heart rate}$$

Statistical analysis

We expressed data as mean $\pm$ standard error of the mean. We used unpaired Student t test to compare baseline characteristics of patients in Group I with those of Group II and between parameters of patients who developed AKI or not. Values of $P<0.05$ were considered significant.

Ethical statement

The Research Ethics Committee of our institution (Comissão de Ética para Análise de Projetos de Pesquisa—CAPPesq, da Diretoria Clínica do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo) approved this study, which follows ethical standards established by the Declaration of Helsinki. All patients wrote and signed an informed consent before enrollment in the study.

Results

Baseline clinical characteristics

Table 1 shows the baseline clinical characteristics of infected cirrhotic patients in Group I and Group II at hospital admission. The mean age of patients was 55.0 ± 1.9 years. There were 11 (61%) males and 7 (39%) females. The etiology of cirrhosis was alcohol in 6 patients (33%), cryptogenic in 4 patients (22%), alcohol associated with hepatitis C in 3 patients (17%), hepatitis C in 2 patients (11%), and other etiologies in 3 (17%) patients. The Child–Pugh score was C in 11 (61%) patients and B in 7 (39%) patients, and Model for End-Stage Liver Disease (MELD) score was 21 ± 1. Furthermore, the baseline clinical characteristics of patients in Group I were similar to those of patients in Group II.

Although we found similar MELD score in both groups, MELD score was higher in patients who developed AKI than those patients who did not (26 ± 1 vs. 16 ± 2, $P=0.001$), at hospital admission. However, both groups showed similar values of C-reactive protein that were 61 ± 19 mg/L vs. 40 ± 12 mg/L in patients with and without AKI, respectively.

As expected, SCr did not allow predicting AKI at 0 hours. SCr values were 1.95 ± 0.37 mg/dL and 1.22 ± 0.29 mg/dL, $P=0.14$