Survey of Serum Procalcitonin in Cirrhotic Patients

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Abstract- Procalcitonin (PCT) is a prohormone that has been used as a marker for the diagnosis of bacterial infections. The aim of this study was to survey PCT levels in patients with cirrhosis. Sixty-four patients with hepatic cirrhosis and 32 healthy blood donors were enrolled in this study. Serum PCT levels was detected using immunoluminometric assay. The rate of positive PCT was higher in patients with hepatitis C cirrhosis (92.8%) than the other groups. Among other cirrhotic patients, positive PCT levels were 77% for hepatitis B, 70% for cancer and 53.3% for unknown groups respectively. Serum procalcitonin levels were significantly higher in cirrhotic patients with bacterial infection (2.65±1.11 ng/ml) than those without infection (0.59±0.16 ng/ml, *P*=0.0001). PCT assay in cirrhotic patients may help diagnosis of sepsis and reduce unnecessary antibiotic use.

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Keywords: Cirrhosis; Infection; Procalcitonin

Introduction

Procalcitonin (PCT) is a 116 amino acid protein, a calcitonin precursor, which is in healthy individuals produced by C type cells of thyroid gland (1). The liver is a key source of PCT. However, production of PCT have been shown in a variety of organs, including liver, lung, kidney, adrenal tissue, monocytes, granulocytes, testis, prostate gland and small intestine (2-4). Procalcitonin levels rise in bacterial, parasite and yeast infections (5). Elevated procalcitonin levels appear only in inflammations of an infectious etiology with systemic signs. Therefore, procalcitonin determination is appropriate for the diagnosis of infections. Half-life of procalcitonin in serum is 20-24 hours, which makes it suitable for daily monitoring. Therefore, it is important in controlling the course of treatment. It can also distinguish bacterial infection from other types of inflammations (6).

Bacterial infections are a major cause of morbidity and mortality among people (7-9). Diagnosis of bacterial infections is sometimes challenging, because clinical manifestations of infections from different causative agents can be similar. For example, it may be difficult to differentiate viral from bacterial infections in different cases (7,9). Incidence of bacterial infections in patients with liver disease is high. Due to a liver dysfunction, immune reactivity is significantly impaired. Therefore bacterial infections including sepsis, bacterial peritonitis, and peptic ulcer with *Helicobacter pylori* origin (10), respiratory tract infections, urinary tract infections and sepsis are more frequent (10-12). Most common characteristic laboratory tests for bacterial infection include test of a number of leukocytes in peripheral blood, differential count of leukocytes, erythrocyte sedimentation rate, procalcitonin, C-reactive protein (CRP), tumor necrosis factor alpha, interleukin-1, interleukin-6, interleukin-8, and complement fragment C3a (5,13). Among several markers of inflammation and sepsis, PCT and CRP markers are highly important in investigating their accuracy for the diagnosis of bacterial infections. Under normal conditions, negligible serum PCT concentrations are usually detected (14). The mechanism proposed for PCT production after inflammation and its role are still not very clear. It is believed that PCT is produced by the liver (15) and peripheral blood mononuclear cells (16), modulated by lipopolysaccharide and sepsis-related cytokines. The aim of our study was to analyze the PCT levels in patients with hepatic cirrhosis who attended the gastroenterology clinic for endoscopy with no apparent sign of infection.

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Materials and Methods

In this study, sixty-four patients with hepatic cirrhosis and 32 healthy blood donors as control group were enrolled. Age and gender distribution was similar between patient and healthy controls. The institution's ethics committee approved the study, and all patients provided written informed consent to participate in this study. Blood samples (5 ml with no anticoagulants) were collected from 64 consecutive patients who complained of dyspeptic symptoms on admission. Blood samples of 32 healthy blood donors were collected as control group. Serum PCT levels were detected using immunoluminometric assay (Brahms Diagnostica GMBH, Berlin, Germany). Detection limit was evaluated as >0.5 ng/ml. Data are expressed as mean ± SD, and statistical analysis was performed using one-way ANOVA. $P<0.05$ was considered as significant difference.

Results

Sixty-four consecutive patients with liver biopsy proven cirrhotic cases were included in this study. Results were compared with 32 healthy volunteers. Figure 1 shows patient distribution according to origin of cirrhosis. The rate of positive PCT was higher in patients with hepatitis C cirrhosis (92.8%) than the other groups. That means serum PCT level in hepatitis C cirrhosis was significantly more than hepatitis B, alcohol, cancer and unknown cirrhosis. Among other cirrhotic patients, positive PCT were 77% for hepatitis B, 70% for cancer and 53.3% for unknown groups respectively. Comparison of PCT levels between patients and controls is shown in table 1.

Serum procalcitonin levels were significantly higher in cirrhotic patients with bacterial infection (2.65±1.11 ng/ml) than in those without infection (0.59±0.16 ng/ml, $P=0.0001$), whereas they were within normal range (<0.5 ng/ml) in all patients without infection, irrespective to the cause of cirrhosis.

Table 1. Comparison of PCT levels (ng/ml) between patients and controls.

Unknown origin cirrhosis	Hepatitis B cirrhosis	Hepatitis C cirrhosis	Alcoholic cirrhosis	Cancer cirrhosis	Control group
1.34 ± 1.11	1.67±0.98	3.11±1.14	0.7±0.26	1.23±1.19	0.51±0.20

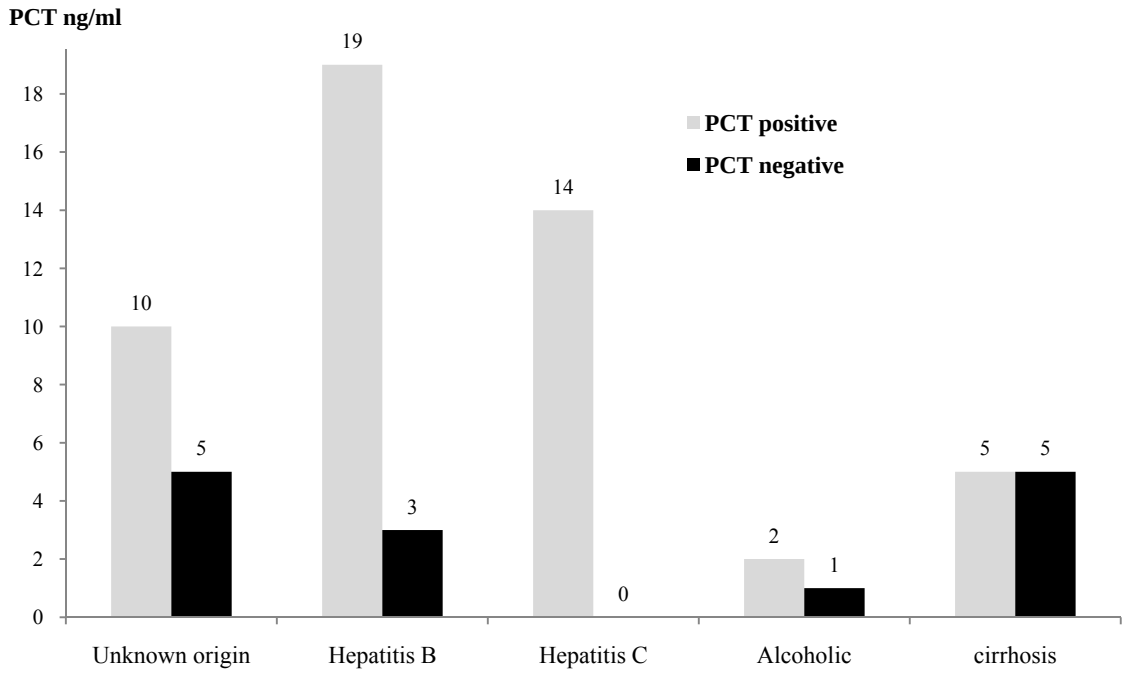

Figure 1. PCT levels in Patients according to origin of cirrhosis.

Table 2. The mean value of ALT, AST, Albumin and Total protein of study population

	Patient	Control
ALT (IU/L)	97.2±32.2	44.3±12.5
AST (IU/L)	88.5±18.3	26.5±13.4
Albumin (g/dl)	3.63±0.34	4.00±0.37
Total protein (g/dl)	5.98±0.59	6.80±0.77

The mean value of ALT, AST, albumin and total protein in patient and control groups are presented in table 2. Liver function profile of the study population indicated a significant rise in serum levels of ALT and AST. Also albumin and total protein levels were lower in patients as compared to healthy controls, but the difference was statistically not significant.

Discussion

Early identification of infections is still a challenge for all clinicians throughout the world. The consensus is not to provide antibiotics for every suspected infection because of emerging issues with bacterial resistance. Therefore, a marker specific for bacterial infection will be most helpful for identification of different types of infections (17).

Bacterial infections are frequently observed in patients with liver disease and are life threatening specially in cirrhotic ones, so early diagnosis is mandatory (18).

Generally, in patients with liver cirrhosis, bacterial and viral infections are more frequent (5,12). They usually include sepsis, spontaneous bacterial peritonitis, infection of the respiratory system, urinary tract infections, and bacteremia. A timely proof of a bacterial infection and an appropriate and effective antibiotic therapy lead to an improvement of the general state of cirrhotic patients and to their better prognosis.

A meta-analysis was performed to evaluate the accuracy of determination of serum PCT and CRP levels for the diagnosis of bacterial infection. PCT level was more sensitive and more specific than CRP level for differentiating bacterial from non-infectious causes of inflammation. Based on this analysis, the diagnostic accuracy of PCT measurement was higher than that of CRP among patients hospitalized for suspected bacterial infections (17). Although diagnostic and prognostic values of serum PCT levels in liver disorders has shown controversies (19).

Our findings indicate significant differences in the serum levels of PCT between healthy control and cirrhotic patients. Surprisingly, the rate of positive PCT was highest among patients with cirrhosis of hepatitis C origin. Cirrhosis is known to be associated with an increased risk of sepsis and sepsis-related mortality. However, blood levels of PCT were lower in patients with alcoholic cirrhosis than in those without, but the differences were not statistically significant.

One interesting finding was that PCT assay might be helpful in identifying infection in patients with different background of cirrhosis. Few studies show diagnostic value of PCT in predicting infection in cirrhotic patients with bacterial infection and they yielded conflicting results. Viallon *et al*. in their study on cirrhotic patients concluded that serum PCT levels might be useful as a marker for the diagnosis of bacterial peritonitis in patients with cirrhosis (20). On the other hand, Spahr *et al*. concluded, on the basis of their findings that PCT levels are inaccurate in these patients (21). In our study, PCT can perform well for diagnosis of infection in patients with cirrhosis.

Although the liver is the main source of PCT, serum levels of this acute-phase protein were significantly higher in patients with hepatic C cirrhosis than the other groups. Therefore, this protein is may also be useful as an indicator of HCV infection in patients with cirrhosis. In conclusion, serum PCT levels may become a useful marker for the diagnosis of sepsis and other infections in cirrhotic patients. The application of assays for PCT might guide monitoring infections, treatment and reduce unnecessary antibiotic use in patients. Based on the results in similar studies elevated PCT levels in patients may help to predict sepsis. Therefore, PCT assessment may potentially help physicians to limit the number of prescriptions for antibiotics.

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