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ORIGINAL ARTICLE

The role of serum intestinal fatty acid binding protein levels and D-lactate levels in the diagnosis of acute intestinal ischemia

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Summary

Background and objective: To evaluate the clinical usefulness of serum intestinal fatty acid binding protein (I-FABP) and D-lactate measurements in the early diagnosis of acute intestinal ischemia.

Methods: A total of 272 patients with a clinical diagnosis of acute abdomen were recruited for this trial over a 24-month period, and 37 healthy people were included in the study as controls. Serum I-FABP and D-lactate levels were measured by an enzyme-linked immunosorbent assay and compared in patients with intestinal ischemia vs. non-intestinal ischemia.

Results: Of the 272 patients, 39 were diagnosed with intestinal ischemia and 233 were diagnosed with other cause of acute abdomen. The mean serum I-FABP and D-lactate levels in the patients with intestinal ischemia were 149.74 ± 57.81 ng/mL and 52.73 ± 26.46 ug/mL, respectively, and were significantly higher compared with patients with non-intestinal ischemia (36.78 ± 11.25 ng/mL and 15.58 ± 5.17 ug/mL, respectively) and with levels in the healthy control group (8.33 ± 6.25 ng/mL and 5.47 ± 1.64 ug/mL, respectively). Area under the curve for I-FABP and D-lactate were 0.85 and 0.69, and cut-off values of 93.07 ng/mL and 34.28 ug/mL, respectively.

Conclusion: Serum I-FABP and D-lactate can improve the diagnosis of intestinal ischemia in patients with acute abdomen who are at risk.

Introduction

Acute intestinal ischemia is a severe intestinal emergency with high morbidity and mortality rates [1]. The causes are broadly divided into two groups, those of vascular origin (mesenteric arterial embolism, mesenteric venous

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thrombosis and non-occlusive intestinal ischemia), the other cause is non-vascular diseases such as bowel strangulation [2]. Early diagnosis of acute intestinal ischemia (usually caused by occlusion of the superior mesenteric artery) remains difficult, however, as the clinical signs that are used for discriminating intestinal ischemia from other causes of acute abdominal pain are not reliable. In addition, current laboratory tests, such as creatine kinase, C-reactive protein, and lactate dehydrogenase (LDH), are not specific biochemical markers for intestinal ischemia [3]. Radiologic diagnostic tests (i.e., computed tomography (CT) and mesenteric angiography) are useful, but the value is limited for early diagnosis because of the diversity of causes leading to acute intestinal ischemia. Therefore, it is important to improve the early diagnosis of acute intestinal ischemia.

Intestinal fatty acid binding protein (I-FABP) is a cytosolic protein with a molecular mass of approximately 15 kDa [4]. I-FABP is limited to mature enterocytes of the small and large intestine and makes up a significant proportion (2%) of all protein in enterocytes at the tip of the intestinal villi [5]. I-FABP is released into the circulation as soon as intestinal mucosal injury occurs. Due to its low molecular mass and abundant and specific localization within the intestinal epithelium, I-FABP may represent a potential serum marker for the diagnosis of intestinal disease.

Some investigators have reported elevation of serum I-FABP levels in patients with occlusion of the superior mesenteric artery [6], strangulated obstruction of the bowel [7], celiac disease [8], necrotizing enterocolitis [9], and ulcerative colitis [10]. These findings suggest that I-FABP values can provide information regarding the extent of intestinal epithelial cell damage. However, the clinical usefulness of I-FABP as a biomarker for intestinal ischemia is uncertain.

D-lactate is produced only by colonic bacteria as a normal byproduct of bacterial fermentation. During ischemia, as the normal mucosal barrier is damaged and permeability increases, a large amount of D-lactate is released through the damaged intestinal mucosa into the peripheral blood, lead to increasing blood levels of D-lactate. Because the liver is unable to metabolize D-lactate, a rise in the serum concentration occurs [11,12]. Some studies have found high levels of serum D-lactate in patients with intestinal ischemia [13,14]. Therefore, D-lactate may also be a useful clinical marker for the early diagnosis of acute intestinal insult.

The aim of this study was to evaluate the clinical usefulness of serum I-FABP and D-lactate measurements in the early diagnosis of acute intestinal ischemia.

Subjects and methods

Ethical considerations

This study was approved ethically by the Institute of the PLA General hospital and written informed consent was obtained from all patients prior to their participation in the study.

Subjects

Between September 2011 and February 2014, 272 patients with a chief complaint of severe abdominal pain requiring surgery, as determined by experienced surgeons, were enrolled in the study. Patients with preexisting intestinal damage due to intestinal surgery, abdominal trauma within 7 days, and colectomy in the history were excluded.

We collected the enrolled patients' blood sample before they accepted treatment. The serum was frozen and preserved until diagnosis was confirmed. We then retrospectively analyzed the serum. Whole blood collected from each patient was immediately centrifuged at $4000 \times g$ for 20 minutes at 4 °C. The separated serum was stored frozen at −80○C until measurement of I-FABP and D-lactate. Diagnosis was based on CT angiography, and findings during surgery or autopsy and verified by histopathological examination of the intestine.

I-FABP and D-lactate were compared with classic biomarkers for intestinal ischemia such as elevated leukocyte count, C-reactive protein, creatine phosphokinase (CPK), and LDH. Blood samples for these reference tests were taken at the same time-point as the samples for measurement of I-FABP and D-lactate. The normal ranges of the biomarkers used in this study were: WBC count, $3.50-8.50 \times 10^9$/L; CRP, < 0.5 mg/dL; CK, 56—244 units/L; LDH, 106—211 units/L.

Serum I-FABP and D-lactate measurements

Serum I-FABP and D-lactate concentrations were determined using standard enzyme-linked immunosorbent assays. Human FABP enzyme-linked immunosorbent assays kits are solid-phase enzyme-linked immunosorbent assays based on the sandwich principle with a working time of 4 hours. The serum I-FABP level of the healthy controls was 8.33 ± 6.25 ng/mL, and the D-lactate level of the healthy controls was 5.47 ± 1.64 ug/mL.

Analysis of diagnostic utility

The serum I-FABP and D-lactate cut-off level for the diagnosis of acute intestinal ischemia were determined by receiver operating characteristic (ROC) analysis on the basis of the data for 272 patients with acute abdomen who were enrolled in the study.

In order to calculate the difference of I-FABP and D-lactate levels in acute intestinal ischemia and other acute abdominal diseases, the group of 272 eligible patients was divided into two subgroups: intestinal ischemia and non-intestinal subgroups. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of both serum I-FABP and D-lactate for the diagnosis of acute intestinal ischemia were also calculated.

Statistical analysis

Mann-Whitney U test was used for the ''between group'' comparisons. All data were represented as median, mean ± SD and range. ROC curves were used to determine the cut-off points of serum I-FABP, D-lactate, leukocyte count, C-reactive protein, CPK, and LDH that most accurately discriminated patients with intestinal ischemia from patients with acute abdomen due to other causes. The ROC curves