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ORIGINAL ARTICLE

Evaluation of Serum Immunoglobulin a Levels in Patient with Suspected Intestinal Ischemia as a Diagnostic Biomarker

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ABSTRACT
Intestinal ischemia, especially in acute mesenteric artery occlusion is still one of the problems in the diagnosis of abdominal pain, due to its high mortality rate did not change. in this study, we evaluated the changing of immunoglobulin A in intestinal ischemia, until if, this biomarker have high diagnostic value in intestinal ischemia be used as a routine clinical test in diagnosis of intestinal ischemia suspended patients in therapeutic center. In this case - control study, the target population ,contain patients with suspected intestinal ischemia were referred to Imam Reza Hospital, Mashhad University of Medical Sciences, were studied in two group, 24 cases and 24 control subjects. In addition to routine intestinal evaluation and resection of necrotic part of intestine we considered IgA serum level by ELISA method as a diagnostic biomarker. The mean age was 64.4 years in study group and 59 years in control group. IgA levels in serum samples from patients of study group was 203 ± 85.5 mg / dl and for the control group was 199.9 ± 59.9, that the difference between the two groups was not significant (P> 0.05). Correlation coefficient of ischemic intestinal length and IgA levels was 0.113. Also, correlation coefficient of time distance between the onset of symptoms to receive patient to the medical center and IgA levels was 0.169. By considering cut off equal to 250 mg / dl for IgA, sensitivity for the diagnosis of intestinal ischemia was 25% and specificity was 66.7%. Positive likelihood ratio was calculated 75% and also Negative likelihood ratio 44.4%. Due to the differences of IgA in the two groups was not significant and also test sensitivity and specificity was low, this biomarker cannot be an effective factor in the early diagnosis of intestinal ischemia, in other side because of incoherent results of previous study and also inadequacy of this study we suggested that larger and absolutely study be perform in future.
Keywords; *Intestinal ischemia, Immunoglobulin A, Diagnosis*

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INTRODUCTION

Mesenteric ischemia occurs in two forms: Acute and chronic. Four distinct pathophysiological mechanisms can lead to this type of ischemia: arterial embolism, arterial thrombosis, vasospasm (also known as non-obstructive mesenteric ischemia) venous thrombosis. The most common cause of acute ischemia is embolism which is responsible for more than 50% of cases. The Source of embolism usually is the heart- often atrial thrombus or left ventricular or valvular lesions [1]. Acute mesenteric ischemia hallmark, regardless of the pathophysiological mechanism is that severity of abdominal pain does not fit with the tenderness on physical examination [2]. The pain is typically a colicky Pain, and more severe in

the middle of the abdomen. Associated symptoms may include nausea, vomiting and diarrhea [3]. Specific Physical findings are usually absent in first stages of the disease so the diagnosis often made at the stage when the patient's intestines seriously attacked. When the outbreak of intestinal infarction occurs, abdominal distension, hematochesia and peritonitis appear [4]. Acute intestinal ischemia is an emergency in abdominal surgery [3]. It may damage intestinal integrity and threaten the patient's life [5].

Chronic mesenteric ischemia is uprising archly. Abdominal pain after eating is the most common symptom which leads to hating food (fear of food) and loss of weight. Often physicians think that a malignant disease is the cause and the patient suffers of chronic pain during the diagnostic period [4].

Bowel ischemia, particularly in cases of acute obstruction of mesenteric artery is still one of the diagnostic problems in abdominal pain and therefore the high mortality rate of this disease in the past 50 years has not changed. Mesenteric arteries selective angiography is yet the gold standard for diagnosis and in patients with risk factors and abdominal pain is necessary [6]. But this method, in addition to being very costly and time-consuming, is not available in all centers [7]. Bio-markers, such as different enzymes like SGOT, SGPT, LDH, and CPK also had been studied for the diagnosis of bowel ischemia, but none of them had a high diagnostic accuracy [5].

Serum levels of IgA, LDH, and ALP was measured in rat models which had been induced intestinal ischemia. The researchers had noticed a severe postoperative decrease in IgA serum levels in comparison to control group, respectively [7].

Recently some studies showed that some mediators like platelet factor 4 and programmed cell death-1 receptor (PD-1) can effect on the IgA secretion in the bowel and cause injury [8, 9].

In this study, we examined changes in serum levels of immunoglobulin A in the intestinal ischemia. If it has a high positive predictive value for diagnosis in intestinal ischemia, it will be used as a clinical test in the diagnosis of patients with suspected bowel ischemia routinely.

MATERIALS AND METHODS

STUDY DESIGN

This study was a case-control survey on patients with an acute abdomen suspected to bowel ischemia. With regard to the results of similar studies (the features provided in previous studies), the minimum sample size for this study was 24 patients in each group respectively.

The Inclusion criteria was Patients with suspected acute ischemic bowel and the Exclusion criteria were immunocompromised patients and Patients who did not consent to participate in the study. Then we explained them how to carry out this study and after obtaining the informed consent, the investigation began.

Because mesenteric ischemia appears with acute symptoms, and as soon as the surgeon suspect of this disease, the patient will directly transferred to the operating room, no test or diagnostic test is routine and only after seeing an ischemic bowel in OR, definite diagnosis will made.The only extreme test we do was checking the IgA levels as a diagnostic biomarker before the surgery.

As noticed, there were two groups in the study: the case group was the patients whose clinical diagnosis after opening the abdomen was "intestinal ischemia". For a definitive diagnosis, pathology samples were taken from these patients. The pathology report should identify these patients as intestinal ischemia. If after opening the abdomen the surgeon had detected no intestinal ischemia, this diagnosis was refused for the patient and he/she was categorized as control group. In these patients, pathological samples were taken like the recent group.

If there was intestinal mucosal ischemia, no evidence of gangrene have been observed during the surgery. So these patients were candidates for second look to confirm the diagnosis. If in the second surgery, the gangrene was not observed in these patients, they were excluded from the study but if gangrene was detected on the second surgery, the patients were part of the case group.

In this study, from both groups, blood samples were taken before entering the operating room.

Once a case is suspected of bowel ischemia, the blood sample for detecting IgA was taken.IgA in serum was measured by ELISA. In this study, out of 48 patients suspected, 24 had positive for this pathology.

STATISTICAL ANALYSIS

At the first step, univariate relationship between variables such as age, histopathological diagnosis and immunoglobulin A serum level and intestinal ischemia was assessed, then in a multivariate analysis, the association between these factors and intestinal ischemia was extracted. After extraction of independent risk factors, their sensitivity and specificity were calculated.

RESULTS

This study was designed and performed by the Cancer Research Center of Mashhad University of Medical Sciences on patients with suspected of bowel ischemia which was referred to Imam Reza Hospital from january2014 To december2014. A total of 48 patients, including 24 patients with intestinal ischemia as the study group and 24 patients without ischemia, as the control group were entered the study.

The youngest participant in the study was 35 years old and the oldest was a 92 years old man.The average age was 61.7 years old (64.4 in the study group and 59 in the control group). Using T-test, it was found that the differences between the two groups was no significant in this respect (P <0.001).

Of the 48 patients, 25 were males and 23 were females. 10 in the case group and 15 in the control group were male. The difference between the two groups using the Chi square test was not significant (P> 0.05).

Average level of Ig A in serum samples was 203 ± 85.5 mg/dl (81 – 390 mg/dl) in case group and 199.9 ± 59.9 (range 107 to 322) in control group, respectively. Analysis of the results using Independent Samples T-test showed that the difference between the two groups in terms of serum IgA levels were not significant (P> 0.05).

Place of bowel involvement was duodenum in 12 patients, the jejunum in 6 cases, the ileum in 3 cases and common in the ileum and colon in 3 cases. Comparison of IgA levels between patients with different areas of involvement using Post Hoc test showed that there was no significant difference between them.

The length of intestinal involvement among patients was 70.33 ± 48.36 cm in averages (15 - 220 cm). The relationship between the length of involvement and serum IgA levels became clear by using the Pearson correlation. The correlation coefficient was 0.113 which represents a poor relationship between these two factors.

The interval between the onset of symptoms and arriving the Medical centre was one of the criteria that were evaluated in this study. The average time it took for the patients was 6.87 ± 2.19 hours (4-10 Hrs). The relationship between this interval between the onset of symptoms to referral to treatment centres and serum levels of IgA by using the Pearson correlation indicates the correlation coefficient of 0.169.

Using ROC curve analysis showed that the sensitivity and specificity of IgA serum level of250 mg/dl was 25% and 66.7% for diagnosis of intestinal ischemia, respectively. Positive and Negative likelihood ratio was 75% and 44.4% respectively.

DISCUSSION

In intestinal ischemia Patients have complaint of abdominal cramping and pain that does not harmonized with the patient's physical examination [3]. Like any other atherosclerotic process, abdominal examination in mesenteric ischemia, may reveal abdominal bruit. In general, none of the signs and symptoms obtained from the history and clinical examination is specific and not helpful in confirming the diagnosis.

In this study, serum IgA level increased in the intestinal ischemia compared to control group, but there was no significant difference between the control group and ischemic bowel group. One reason could be that most of IgA secreted in the intestinal tractis IgA which is excreted through the gastrointestinal tract.

There was a poor correlation between patient arrival time to the emergency room and IgA levels. It is probably because the half-life of IgA (2 to 3 days) (thus it remain relatively stable in this period [10].

Since the amount of immunoglobulin A in adults should be about 250 mg per one hundred millilitres of serum, we take it as cut-off point. The estimated sensitivity and specificity was 25% and 66.7% for diagnosis of intestinal ischemia which suggests that this factor would not be very dedicated and helpful.

In an animal study, the level of serum IgA in rats with ischemia greatly reduced one hourafter operation compared with control [7].

It has recently been shown that some mediators are responsible for tissue damage in intestinal ischemia due to a probable effect on IgA secretion.

For example some researchers showed that the programmed cell death-1 receptor (PD-1) plays a crucial role in regulating intestinal secreted IgA (sIgA). In a rat model, PD-1/PD-L1, TGF-β1, and IL-21 expression was down-regulated after intestinal ischemia and IgA (+) B cells were decreased consequently [9].

Some studies show that other chemical mediators like platelet factor 4 may play a role in extensive tissue injury after ischemia and can modulate the release of IgA in GI tract [8].

CONCLUSION

Because intestinal ischemia can quickly go to fatal intestinal infarction, in case of doubt, impact diagnosis and treatment is of utmost importance. So the need for a quick, cheap and accessible diagnostic method is essential for early detection of ischemia. In our study, the differences between the two groups was not significant and IgA test sensitivity was low and could not be used as a factor in the diagnosis of intestinal

ischemia. Because of conflicting results obtained, compared with previous studies, more comprehensive and complete studies in the future are recommended.

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