Ann Med Res

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Annals of Medical Research

journal page: www.annalsmedres.org

Comparison of C-reactive protein and high-sensitivity C-reactive protein in acute appendicitis patients with normal white blood cells counts

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ARTICLE INFO

Keywords:
Acute appendicitis
C-reactive protein
High-sensitivity C-reactive protein

Received: Apr 20, 2022
Accepted: Jul 26, 2022
Available Online: 27.09.2022

DOI:
10.5455/annalsmedres.2022.04.135

Abstract

Aim: Acute appendicitis (AA) is one of the main causes of acute abdominal pain. The main goal of treatment is early diagnosis and emergency surgical intervention. Late diagnosis leads to complex acute appendicitis (gangrene, abscess, and perforation). Although the signs and symptoms of acute appendicitis are well known, it is sometimes difficult to diagnose. Various laboratory markers have been studied for the diagnosis of acute appendicitis, but none showed superiority over physical examination or imaging. In addition, the superiority of high-sensitivity C-reactive protein (hs-CRP) over C-reactive protein (CRP) in patients diagnosed with acute appendicitis has not been evaluated in any study to date. With the current study, we aimed to compare CRP and hs-CRP values in patients with acute appendicitis whose white blood cells (WBC) are in the normal range.

Materials and Methods: In this study, serum levels of CRP and hs-CRP were measured in 45 patients with acute appendicitis (who had normal WBC values) and 42 healthy controls. The results obtained were statistically evaluated in terms of significant differences between the two study groups. In addition, ROC (Receiver Operating Characteristic) analysis was performed to determine the power of CRP and hs-CRP in the differential diagnosis of acute appendicitis.

Results: CRP and hs-CRP levels of the patient group were significantly higher than the control group (0.002 and <0.001 respectively). ROC analysis results revealed that hs-CRP has higher diagnostic power than CRP in discriminating between AA patients and healthy people.

Conclusion: This study showed that hs-CRP may be a more effective biochemical marker in the diagnosis of acute appendicitis instead of CRP.

Introduction

Acute appendicitis (AA) which is accepted as one of the most common causes of emergency abdominal surgeries is diagnosed quite hardly even by most experienced surgeons and negative laparotomy rates are between 20-30%. The main aim of treatment is early diagnosis and emergent surgical intervention. When left untreated, inflammation and cause abscess formation and perforation followed by peritonitis, and on the other hand, negative laparotomy may cause intestinal obstruction in about 5% of patients [1]. Late diagnosis causes complex AA (gangrene, abscess, and perforation). Gangrene and perforation are among the dangerous complications of AA and can be presented in almost 40% of cases. Although the signs and symptoms of AA are well known, it is sometimes hard to diagnose. Together with this, clinical symptoms, physical examination findings, and radiological features are not specific for determining the degree of disease. It is critical to discriminate between non-specific belly aches and appendicitis. Additionally, the radiological test is high cost and especially causes high radiation exposure, especially in the pediatric population [2, 3]. The negative laparotomy rates in AA have caused an increase in the need for laboratory tests in the diagnosis of acute disease.

The most frequently used parameter in AA diagnosis is leukocytosis. Diagnosis with a single laboratory test is difficult for AA diagnosis. Besides these, a delay in diagnosis may cause serious morbidity, mortality, and complicated appendicitis. Leukocyte count (WBC) is one of the tests used for the diagnosis of acute appendicitis, and it helps to decide if the patient will receive antibiotic treat-

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ment or surgical intervention. Another helper test is an acute-phase protein, C-reactive protein (CRP) released by hepatocytes. Various studies have shown that CRP levels are helpful in AA diagnosis as its levels rise in early inflammation. CRP is a commonly used test, especially in suspicious inflammatory situations. CRP was classified as an "acute phase protein" in the 1930s and since then it has been widely used as a screening test for tissue inflammation, a biomarker of disease activity, and a predictive marker in many acute and chronic infections. CRP is also a useful reference in the clinical decision of patients with abdominal pain with its 89% specificity and 88% positive predictive value. CRP has found a place together with WBC in AA diagnosis as a biochemical marker and serial CRP measurements can be accepted as a tool in discrimination between non-perforated and perforated appendicitis. High sensitivity CRP (hs-CRP) is more sensitive than conventional CRP when measuring normal concentrations and provides a better measure of inflammation [1, 2, 3]. Despite this, it is not known how much benefit hs-CRP will provide if used in AA, and as far as we know, there is no previous study focused on this subject.

In the present study, we aimed to compare CRP levels used routinely in AA patients with hs-CRP levels which is a much more sensitive marker, especially in lower limits. That's how we will be able to decide if hs-CRP is more advantageous in AA diagnosis than conventional CRP.

Materials and Methods

Patient population

The study has been approved by local ethics committee. (Decision date/no: 15.12.2021/2021-55). The patients included in the study were selected among those who applied to Ankara Gülhane Training and Research Hospital General Surgery Clinic between 20 December 2021 and 25 March 2022. Written informed consent was obtained from all participants and done red capped tube of blood was collected from each. Serum samples of patients with acute appendicitis diagnosis were used. Patients with normal WBC levels at admission were included in the study. The following characteristics were sought in the individuals included in the control group; 1. Not having acute appendicitis, 2. Not having any chronic disease, 3. Routine examinations are within normal limits, 4. Not to smoke and alcohol, 5. To be between the ages of 18-90, 6. To agree to be included in the study. Power analysis was performed to determine the minimum sample size. Accordingly, the minimum sample size was determined as 50 people in total, with 25 patients and 25 control groups. A total of 87 participants, including 45 patients and 42 control groups, were included in the study.

Analytical methods

One red-capped tube was obtained from all participants and centrifuged within one hour to separate sera. Separated sera were stored in Eppendorf tubes at -80 0C until the time of analysis. All specimens were melted at room temperature for 30 minutes before analysis. All patient and control specimens were run in the same batch at Beckman Coulter AU680 autoanalyzer by immunoturbidimetric method to detect CRP and hs-CRP levels. Demographic and anthropometric features of patients were driven by the hospital information system.

Table 1. CRP and hs-CRP values in patient and control groups.

Parameters	Patient	Control	p value
CRP (mg/L)	8.10 (1.00-210.90)	3.95 (2.00-21.20)	0.002*
hs-CRP (mg/L)	7.00 (0.6-160.50)	2.15 (1.00-15.72)	<0.001*

CRP: C-Reactive Protein, hs-CRP: High Sensitivity C-Reactive Protein. p<0.05 was considered statistically significant. *p indicates significant difference between groups for parameters. Values are given as median (min.-max.). Referenge range; CRP: <5 mg/L, hs-CRP: <1 mg/L. Measuring range; CRP: 1.0-480 mg/L, hs-CRP: 0.2-160 mg/L.

Table 2. ROC analysis data of CRP and hs-CRP.

Parameters	Cutoff	Sensitivity	Specificity	p value	AUC
CRP (mg/L)	5.24	66.7	66.7	0.001	0.700
hs-CRP (mg/L)	3.05	77.8	76.2	<0.001	0.820

CRP: C-Reactive Protein, hs-CRP: High Sensitivity C-Reactive Protein, AUC: Area under the curve. p<0.05 was considered statistically significant.

Statistical methods

IBM SPSS 22.0 program (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.) was used for statistical analyses. Normality tests were done with the Shapiro-Wilks test. Parametric variables are expressed as mean and standard deviation (SD) while non-parametric variables were expressed as median and min-max values. Independent samples t-test was used for parametric variables while Mann-Whitney U test was used for non-parametric ones. $p<0.05$ was accepted as the limit of statistical significance for all variables. ROC (Receiver Operating Characteristic) curves were constituted for analysis of the discrimination strength of each parameter between patients and healthy subjects.

Results

Tweenty-three females and 22 males (age; 30.82±6.42) were found in the patient group and, 22 females and 20 males (age; 32.69±7.56) were found in the control group. The hospital stay of patients was around 1.76 days. Due to ultrasound images, 10 of the patients were normal, 29 were non-perforated and 6 were perforated. 18 patients had open, while 27 had a laparoscopic operation. Histological evaluation revealed that 1 patient was subacute, 17 were acute oedematous, 14 were acute flegmanteous, 1 was fibrous obliteration diverticulitis formation, and 4 were lentoid hyperplasia, 6 were acute necrotizing, and 2 were acutely perforated. Table 1 summarized the CRP and hs-CRP values in patient and control groups. Table 2 summarizes ROC analysis results.

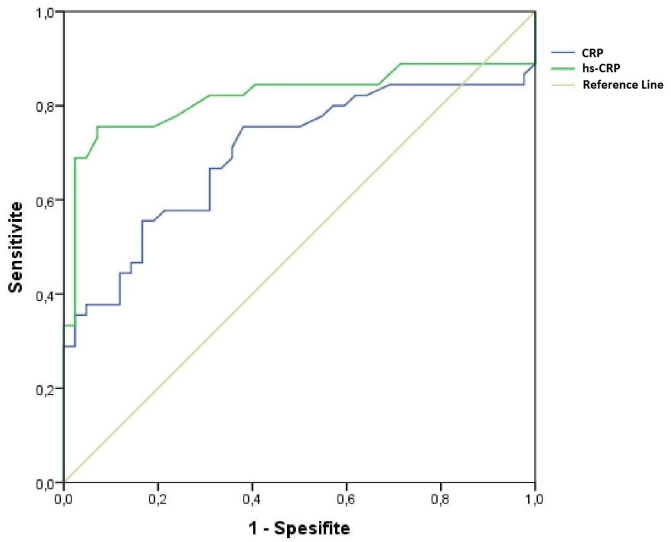

Figure 1. ROC curve of CRP and hs-CRP for discrimination of acute appendicitis patients and healthy individuals.

Discussion

Acute appendicitis is the most common indication for emergency surgery in all age groups. The first clinical presentation is the perforation of the appendix, especially in the elderly. Negative appendectomy ratios are still high despite various radiological imaging, biochemical tests, and scoring algorithms (4). Laboratory findings together with clinical symptoms may help AA diagnosis. Together with this, when clinical and laboratory variables are evaluated as a whole, they provide high discriminatory power, but when evaluated individually, they provide a poor prediction [5, 6].

There have been various trials to decrease negative laparotomy rates in clinically suspected AA. Unfortunately, there is no specific diagnostical test for AA. WBC count is most commonly used for AA diagnosis in the laboratory. An increase in WBC number is not directly proportional to AA severity and it is also not rigid and not reliable in predicting disease severity [5, 7].

Previous studies have revealed that elevated CRP together with leukocytosis provides a better diagnostic value for AA. In AA, especially in the first 12–24 hours, serial increases in CRP are considered valuable [8, 9]. Although CRP is a valuable marker in abdominal paint has to be combined with CT results and clinical evaluations. A meta-analysis reviewing the diagnostic accuracy of CRP has revealed a very wide range of sensitivity and specificity (47-74% and 55-89% respectively) [9]. CRP levels alone do not approve or exclude AA diagnosis.

As indicated in the literature, inflammatory markers can be helpful when deciding on operative treatment [10]. hs-CRP has been a search topic in the evaluation of cardiac failure and the severity of pre-eclampsia [11, 12]. The predictive values of inflammatory markers have also been searched in discriminating between complicated and non-complicated diverticulitis [13].

So it can be proposed as a better diagnostic marker for AA when compared to CRP. Besides WBC and CRP, various biochemical and hematological parameters (mean thrombocyte volume, leukocyte/leukocyte ratio, interleukins (IL)-6, IL-10, IL-4, IL-5, IL 12, tumor necrosis factor-alpha (TNF-a), endotoxin, erythrocyte sedimentation rate, procalcitonin, fibrinogen, alpha 2-macroglobulin, alpha 1 antitrypsin, D-lactate) have been studied. However, none of them have found a place in routine applications [14]. New biochemical markers for the prevention of negative laparotomy rates as well as for the early detection of AA are still of interest. In the present study, hs-CRP levels of patient and control groups were significantly different. These data give us the idea that hs-CRP, instead of CRP is a stronger marker in the discriminative diagnosis of AA. The cure of appendicitis with antibiotics instead of surgery has been a topic of focus all around the world. Data has been driven as antibiotics can cure 80% of AA patients as a trustable and effective treatment method [15, 16]. But the effectiveness of treatment with antibiotics at which severity level of the disease is still unknown. That's why reliable markers are needed to discriminate between suspected, complicated, or non-complicated appendicitis. hs-CRP can be useful in these terms. As it is a routinely used laboratory marker, it is convenient for fast and accurate analysis. To our knowledge, this is the first report in the literature that evaluates the effectiveness of CRP and hs-CRP in patients with normal WBC counts. This can be accepted as a preliminary study.

This study showed that hs-CRP may be a more effective biochemical marker in the diagnosis of AA instead of CRP. An additional study may be planned to discuss the difference in a larger working group. This can be considered a pioneer work in understanding the role of hs-CRP in AA.

Ethics approval

The study was obtained from Gülhane Training and Research Hospital Ethics Committee, (Decision date/no: 15.12.2021/2021-55).

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