Research Article

Comparison of Serum Inflammatory Markers and Alvarado Score in Diagnosing the Acute Appendicitis: A Prospective Multi-Center Study

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ABSTRACT

OBJECTIVE: Despite substantial advances in diagnostic assessments of patients with infectious and inflammatory diseases, the role of these evaluations is still unclear in patients with acute appendicitis. Comparing the role of different laboratory tests in diagnosis of acute appendicitis may help to find a more accurate diagnostic protocol in these patients.

METHODS: This prospective study evaluates the diagnostic accuracy of 3 serum inflammatory markers (leukocytosis, C-reactive protein, procalcitonin), individually and in combination with each other and Alvarado score in 50 patients with normal appendix and 70 patients with acute appendicitis (according to their histopathology report).

RESULTS: Maximum diagnostic accuracy (84.16%) was seen in Alvarado ≥7, individually. Alvarado ≥5 had 70% accuracy in diagnosing the acute appendicitis individually but Alvarado ≥5 in combination with procalcitonin level >0.05ng/dl had an accuracy rate of 80% and the maximum negative predictive value (93.33%). Combination of three inflammatory markers showed an accuracy of 75.83%. Leukocytosis, C-reactive protein and procalcitonin had the accuracy rates of 64.16%, 70% and 75.83% respectively. Highest sensitivity (97.14%) was seen in combination of Alvarado ≥5 and procalcitonin/C-reactive protein. Alvarado score ≥7 had the highest specificity (79.5%).

CONCLUSION: In patients with Alvarado score ≥7, further laboratory assessments may be obviated. In patients with Alvarado score ≥5, measuring the procalcitonin level may help the physician to rule in or rule out the acute appendicitis. Among the three studied inflammatory markers, serum procalcitonin level had the highest accuracy.

Keywords: Diagnostic accuracy, Acute appendicitis, Procalcitonin, C-reactive protein, Leukocytosis

INTRODUCTION

Despite substantial advances in laboratory evaluation of patients with acute appendicitis, the practical role of these studies is unclear and negative appendectomy has still a rate of more than 10% in most studies (both in children and adults) (1-3). Currently, laboratory tests are used as adjuncts to clinical and/or radiological assessments in patients with unusual presentation. Beside some traditional tests commonly used in assessing the patients with right lower quadrant pain (like complete blood count), some new tests are also introduced in recent years to improve the diagnostic accuracy of laboratory studies in patients suspicious to

acute appendicitis. Procalcitonin and C-reactive protein (CRP) are two examples of these relatively novel tests.

CRP is an acute phase reactant protein made by hepatocytes and raised within 6 to 8 hours after beginning of an infectious/inflammatory process including acute appendicitis (4). Although some studies have shown that CRP levels increase parallel to the severity of acute appendicitis as very high levels of CRP may be an indicator of perforation, gangrene or abscess (5,6), its diagnostic sensitivity and specificity for acute appendicitis differs from 40% to 94% and 38 to 87%, in different studies (7,8). PCT is a glycoprotein which is found only in the thyroid gland under normal conditions as inactive precursor of calcitonin but enters the blood and rises in proportion with the severity of the infection during the inflammatory responses to microbial infections and some other inflammatory responses (9-11).

Diagnostic role of CRP and procalcitonin has been evaluated in different studies recently but the results are conflicting and most of them are focused on each test individually. We conducted a prospective multi-center study to evaluate the accuracy of a combination of serum inflammatory markers including procalcitonin, C-reactive protein and leukocytosis in diagnosis of acute appendicitis both individually and in combination with each other and Alvarado score (as an indicator of clinical findings). Our diagnostic gold standard was histopathology report on specimens obtained during open appendectomy.

METHODS
Study design and setting
This prospective multi-center study was conducted in 3 referral teaching hospitals with annual emergency department visits between 40,000-70,000. Institutional ethics committee (faculty of medicine, Iran University of Medical Sciences) approved our study which was carried out in accordance with Declaration of Helsinki (1989). Informed written consent was obtained from all patients or their legal guardians. We enrolled cases between December 2013 and November 2014, conveniently.

Participants
Patients at any age with primary diagnostic impression of acute appendicitis (according to history and physical examination) were eligible to participate in study. We excluded pregnant women; patients with any other known infectious or inflammatory condition which would raise the serum inflammatory markers (including patients under antibiotic therapy); patients who had alcohol or substance addiction; patients with histopathology report other than acute appendicitis; patients with previous history of appendectomy and patients who left the hospital before surgery.

Intervention
History taking and physical examination were done by on duty emergency physician. Oral temperature >37.8°C was defined as fever. In doubtful cases, the physical examination was rechecked with a general surgeon. Results of clinical assessments were documented by a research assistant.

Venous blood samples were immediately taken for measuring procalcitonin level, CRP level and white blood cell count (WBC). White blood cells were counted by the Hematology Analyzer HARIBA ABX Micros 60 (manufactured by HORIBA ABX SAS, USA). WBC count >10,000 cells/ μL was defined as leukocytosis. The neutrophils percentage >75% was considered elevated. Procalcitonin level was measured by B.R.A.H.M.S PCT kit (from B.R.A.H.M.S Diagnostica, Berlin, Germany). CRP level was calculated by latex agglutination test using Agappe SeroCHEK (manufactured by AGAPPE Hills, India). Serum procalcitonin >0.5 ng/ml and CRP levels >1 mg/dl were considered abnormally high.

Other laboratory and radiological investigations were done for each patient according to diagnostic strategies scheduled by on duty physician.

Patients were followed up and those undergoing open appendectomy were included. The diagnosis of appendicitis was confirmed by the presence of the histological evidence of

appendicitis. Clinical and laboratory findings were compared in 2 groups of patients (based on their histological diagnosis): 50 patients with normal appendix, 70 patients with acute appendicitis.

Data Analysis

Descriptive data are reported as mean (±standard deviation), maximum and minimum. Categorical data are presented with percentages and 95% confidence intervals. Continuous variables with a normal distribution are compared with student's t-test. Chi-square test is used for comparing categorical variables. Sensitivity, specificity, positive and negative predictive values of inflammatory markers (procalcitonin, CRP, WBC count) are calculated individually and in combination with each other and with clinical findings. We used Alvarado scores of 5 and 7 as cut off points because according to previous systematic reviews Alvarado score is a useful diagnostic tool to rule out the appendicitis for all patient groups at a cut point of 5 and to rule in it at cut point of 7 (12). All data analyses are performed with SPSS version 18 (SPSS, Inc., Chicago, IL).

RESULTS

161 patients were assessed for eligibility. 5 pregnant woman, 6 patients with other known infectious condition (1 acute sinusitis, 3 pelvic inflammatory disease, 1 urinary tract infection, 1 pharyngitis), 3 patients with opium/substance addiction, 8 patients with final diagnosis other than acute appendicitis (6 ruptured ovarian cyst, 1 ovarian torsion, 1 colon mass with partial obstruction), 6 patients with previous history of appendectomy, 5 patients who left the hospital before surgery and 8 patients who refused to participate in study were excluded. 120 patients were included and analyzed.

Baseline data

Mean age of patients was 24.76 (±6.75) years old with a minimum of 15 and maximum of 56 years old. 15 (12.5%) of patients were <18 years old. 1 (0.8%) of patients was above 40 years old.

41 (34.2%) of patients were female and 79 (65.8%) were male.

All patients were admitted in ED with complaint of right lower quadrant pain. 90 (75%) of patients had reported a shifting pain. The most common complaints after abdominal pain were anorexia and nausea/vomiting which were seen respectively in 105 (87.5%) and 92 (76.7%) patients. 4 (3.3%) of patients had a history of previous pelvic surgery. 3 (2.4%) had a history of previous cesarean section. 1 (0.8%) of patients had type I diabetes mellitus. 1 (0.8%) had a history of epilepsy. 3 (2.4%) had a history of previous renal colic. No other significant past medical history was documented.

The most common findings in physical examination of patients were right lower quadrant tenderness and rebound tenderness which respectively seen in 116 (96.7%) and 92 (76.7%) of patients. Guarding was seen in 10 (8.3%) patients. Rovsing's, obturator, psoas and Dunphy's (cough) signs were seen respectively in 48 (40.0%), 40 (33.3%), 26 (21.6%) and 37 (30.8%) patients. Fever was documented in 43 (35.8%) of patients. Other basic findings are summarized in table 1. Main results on laboratory tests and their diagnostic value is summarized in tables 2 and 3.

DISCUSSION

Our study showed that serum inflammatory markers have accuracies between 64% and 75% in diagnosing the acute appendicitis. Among the three markers evaluated in this study, procalcitonin had the highest sensitivity, specificity, positive and negative predictive values. Leukocytosis (which has also 2 scores in Alvarado system) has a positive predictive value of 74%. This means that the presence of leukocytosis can guide the physician to the diagnosis of acute appendicitis but its absence has limited role in ruling it out. CRP is a more sensitive test than leukocytosis with more value in ruling out the appendicitis but its overall accuracy is still 70% which shows that CRP level can help acute care physicians to know that an active infectious/inflammatory process like acute appendicitis exists currently in the body

but it can't be used singly in final disposition of patients. Procalcitonin is used commonly in detecting the bacterial infections in different groups of patients. It showed 80% sensitivity and 83% positive predictive value in diagnosing the acute appendicitis in our study but its negative predictive value was as low as 67%. This means that the role of high serum procalcitonin level in ruling in the appendicitis is more accurate than the role of low calcitonin level in ruling it out.

Combining the CRP with leukocytosis or procalcitonin level could not significantly increase the accuracy of tests. Combination of leukocytosis and procalcitonin had also increased the accuracy of procalcitonin test as low as 2%. This is while the combination of triple serum inflammatory markers had the accuracy equal to procalcitonin but with a notably higher sensitivity (93%) and negative predictive value (88%).

We used the results of systematic review by Ohle et al and chose the Alvarado scores of 5 and 7 as the cut off points in assessing the diagnostic value of Alvarado score which consists both the clinical findings and two laboratory ones (leukocytosis and neutrophil dominancy). According to our results Alvarado ≥7 had the highest overall diagnostic accuracy (84%) in diagnosing the acute appendicitis and its sensitivity and positive and negative predictive value were all above 80%. This means that in patients with Alvarado ≥7, further laboratory and radiological assessments can increase the accuracy of decision just by 16%. Alavarado ≥5 was a sensitive measure but its overall accuracy was 70%. Adding the CRP to Alvarado ≥5 increased its accuracy to 71% but joining the procalcitoin level to Alvarado ≥5 could increase the overall accuracy to 80%. These findings show that in patients with Alvarado ≥7 measuring the more inflammatory serum marker levels do not help surgeons significantly but measuring the procalcitonin level in patients with Alvarado ≥5 can more clarify the situation and lead to more accurate patient dispositions.

Our results about the leukocytosis and CRP are against the results of some other studies which show 100% specificity and positive predictive value for the combination of leukocytosis and CRP in diagnosing the acute appendicitis (13) and suggest that patients with right lower quadrant abdominal pain can be safely discharged home from emergency department if they have normal WBC count and CRP level (14). We found that the increase in CRP levels with or without leukocytosis is not adequate to make the diagnosis of acute appendicitis and this is similar to the findings of studies which show that although CRP level may differentiate between complicated (perforated, phlegmonous, abscessed) and non-complicated appendicitis but it can't be used solely in diagnosing the acute appendicitis (15-17).

Our results about procalcitonin alone and in combination with other inflammatory markers also show that theses markers have not enough sensitivity and diagnostic value to diagnose the acute appendicitis accurately. These findings are compatible with the findings of the studies which showed that not CRP nor PCT or D-dimer are good markers for the diagnosis of acute appendicitis (18-19) or the results of Vaziri et al which showed that routine procalcitonin measurement as a diagnostic test for adult patients with acute appendicitis is not cost effective and conclusive and procalcitonin is more a prognostic marker of infectious complications than a diagnostic laboratory test (20).

Limitations

We focused on three serum inflammatory markers in our study but there are also other laboratory tests (like serum bilirubin level) (21) that are proposed to be done in patients suspicious to acute appendicitis. We used Alvarado scoring system as a measure of patient's clinical condition, but other studies may be conducted with more focused approach to determining the diagnostic value of different combinations of clinical and laboratory parameters. We did not gather the data on the time lag between onset of the patient's

symptoms and measurement of markers level and the time of surgery. Unfortunately we also did not compare the inflammatory serum marker levels in patients with complicated and non-complicated appendicitis. Neglecting the role of radiological assessments and repeat blood testing in diagnosing the acute appendicitis in studied patients is also a weakness in our study.

CONCLUSION

In patients with Alvarado score ≥7, further laboratory assessments may be obviated. In patients with Alvarado score ≥5, measuring the procalcitonin level may help the physician to rule in or rule out the acute appendicitis. Among the three studied inflammatory markers, serum procalcitonin level had the highest accuracy in diagnosis of acute appendicitis.

Conflict of interest statement

The authors have no conflict of interest.

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Table 1. Basic findings in studied patients

Variable	Minimum	Maximum	Mean (±SD)
Vital signs			
Oral temperature, °C	36.50	39.40	37.6 (0.6)
Systolic Blood Pressure, mmHg	110	130	119.17 (±8.46)
Diastolic Blood Pressure, mmHg	70	90	78.8 (± 6.2)
Heart Rate, beat per minute	78	84	78.9 (6.7)
Respiratory Rate, respiration per minute	12	16	14.4 (±1.2)
Arterial Oxygen Saturation, (%)	96	98	97.2(±0.7)
Laboratory tests			
Hemoglobin	10.7	16.4	13.3(±1.2)
White blood cell	7400	26000	15203.8(±3450.1)
Platelet	150,000	310,000	204.7(±47.46)
Blood urea nitrogen	12	25	17.9(±4.4)
Creatinine	1	1.7	1.2(±0.2)
Sodium	129	135	132.0(±1.7)
Potassium	4	4.9	4.1(±0.2)
Blood sugar	90	210	130.7(±37.1)
C-reactive protein	0.02	262	31.6(±40.5)
Procalcitonin	0.001	7.08	0.46(±0.9)

Table 2. Comparison of laboratory test results in patients with normal appendix and appendicitis

Variable	Normal appendix group (n=50), Mean (±SD)	Acute appendicitis group (n=70), Mean (±SD)	P value
Procalcitonin	0.04 (±0.01)	0.59 (±0.95)	0.00
C-reactive protein	10.64 (±8.43)	46.73 (±46.52)	0.01

White blood cell	9971.20 (±2692.98)	12330.71 (±3926.99)	0.00
Neutrophil percentage	63.30 (±8.64)	78.77 (±8.49)	0.00
Hemoglobin	12.65 (±0.81)	12.42 (±1.29)	0.92
Platelet	198.31 (±53.51)	204.69 (±46.66)	0.49
Blood urea nitrogen	18.12 (±5.11)	17.94 (±4.31)	0.33
Creatinine	1.18 (±0.25)	1.23 (±0.26)	0.47
Sodium	132.06 (±1.84)	132.04 (±1.78)	0.87
Potassium	4.11 (±0.13)	4.17 (±0.17)	0.14
Blood sugar	118.25 (±29.60)	132.72 (±37.90)	0.15

Table 3. Diagnostic values of serum inflammatory markers individually and in combination with Alvarado score

Test variable	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Overall accuracy (%)
Leukocytosis	58.57	72	74.54	55.38	64.16
CRP	78.78	56	71.79	66.66	70
Procalcitonin	80	79.59	83.87	67.24	75.83
Leukocytosis+CRP	82.42	50	68.08	76.92	70
CRP+Procalcitonin	85.71	50	70.58	71.42	70.83
Leukocytosis+Procalcitonin	88.88	58	75.29	82.85	77.5
Leukocytosis+CRP+Procalcitonin	93	55	71.76	88.23	75.83
Alvarado ≥ 7	88.57	78	84.93	82.97	84.16
Alvarado ≥ 5	85.71	48	69.76	70.58	70
(Alvarado ≥ 5)+Procalcitonin	97.14	56	75.55	93.33	80
(Alvarado ≥ 5)+CRP	97.14	36	68	90	71.66