

ORIGINAL RESEARCH

An Observational Study on C-Reactive Protein as a Diagnostic Parameter in Acute Appendicitis

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ABSTRACT

Background: Although appendicectomy is the most commonly done emergency surgery still its diagnosis remains an enigmatic challenge, with persisting high rate of negative explorations. **Objective:** The objective of the study was to evaluate the role of accuracy of CRP measurement in the diagnosis of acute appendicitis and to reduce the morbidity by avoiding negative exploration.

Materials and Methods: The present study was conducted in 30 patients who have been clinically diagnosed by Surgeon's as having acute appendicitis and posted for emergency appendicectomy in General Surgery Department, Glocal Medical College & Super Speciality Hospital. Preoperatively blood was sent for CRP estimation, after operation, all specimens were sent for histopathological examination, results of CRP were correlated with HPE reports to evaluate their role in diagnosis of acute appendicitis.

Results: In present study, 24 patients had elevated serum CRP level (>2.5 mg/dl) which is 83.3% of total study group. In these patients only one patient had high serum CRP level inspite of normal appendix that was proved histologically. The cause of raised serum level of CRP in this patient was mesenteric lymphadenitis which was found peroperatively. Hence it was proved that CRP level can be used to rule out negative appendicitis, so that surgery can be deferred in them and to reduce rate of negative appendicectomies.

Conclusion: We continue to stress that history and clinical examination by a skilled surgeon still remain indispensable in diagnosing acute appendicitis, and its importance cannot be under mined. But CRP helps to reduce negative appendicectomy rate drastically and hence should always be included in diagnostic work up of acute appendicitis.

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INTRODUCTION

Appendicitis is a condition characterized by inflammation of appendix. The crude incidence of acute appendicitis was 86 per 100,000 per year. Although the incidence of nonperforated appendicitis was highest among adolescents and young adults (13-40 years of age), perforated appendicitis occurred at almost the same incidence in all sex and age groups. Acute abdominal pain is one of most common surgical emergencies. Appendicitis remains the most common abdominal surgical emergency with a life time prevalence of one in seven. There is no reliable specific marker for acute appendicitis and is a reminder for the art of surgical diagnosis. It has been shown that appendicular abscess occurs in 2-6% and appendicular perforation in 25.8% of untreated patients. In the continued absence of a 100%

accurate test for appendicitis, any investigation that can contribute to its diagnosis is valuable.^[1-4]

C-reactive protein is an acute phase reactant, which rises rapidly in response to tissue injury and can be measured in serum 6-12 hours after the onset of inflammation. Many studies have investigated the role of CRP in improving the diagnosis of acute appendicitis, with promising results.^[3-5] Tillet and Francis in 1930 first described C-reactive protein. They demonstrated that CRP could bind to C-polysaccharide of streptococcus in acute phase sera. CRP was discovered in the Avery laboratory of Rockefeller institute. C-reactive protein has been a measure of the acute phase reaction to inflammation for the last 20 years recently improved highly sensitive and standardized quantitative assay in serum and CSF have allowed a reevaluation of its potential as a diagnostic laboratory test.

C-reactive protein is an abnormal serum glycoprotein produced by the liver during the acute inflammation. Because it disappears rapidly when the inflammation subsides its detection signifies the presence of a current inflammatory process. CRP production is a non-specific response to disease and it can never on its own be used as a diagnostic test. However if CRP results are interpreted in the light of full clinical information on the patient, then it can provide exceptionally useful information. CRP is a cyclic pentameric protein composed of five non-covalently bound, identical 23.5 kDa subunits, arranged in a doughnut-shaped polymer. The main function of this pentamer is related to the ability to bind biologically significant ligands in vivo. Tillet and Francis first described protein in 1930. They concluded that sera of patients suffering from acute and reactive infection precipitated with a non-proteic pneumococcus extract called C polysaccharide in the presence of calcium ions. The protein that caused this reaction was therefore called C reactive protein. The function of CRP is related to its role in the innate immune system. Similar to immunoglobulin IgG, it activates complement, binds to Fc receptors and acts as an opsonin for various pathogens. Interaction of CRP with Fc receptors leads to the generation of pro inflammatory cytokines that enhance inflammatory response. Unlike IgG, which specifically recognizes distinct antigenic epitopes, CRP recognizes altered self and foreign molecules based on pattern recognition.^[5-8]

Thus, CRP is thought to act as a surveillance molecule for altered self and certain pathogens. This recognition provides an early defence and leads to a pro inflammatory signal and activation of the humoral, adaptive immune system. CRP binds to molecular groups found on a wide variety of bacteria and act as an opsonin. CRP may also be important in the recognition of necrotic tissues. CRP binds to apoptotic cells, protects the cells from assembly of the terminal complement components, and sustains an anti-inflammatory innate immune response. In man, the only CRP gene coding sequence is found on Chromosome 1. The liver synthesizes CRP. Synthesis of CRP and other acute phase proteins by hepatocytes is modulated by cytokines. Interleukins 1 b and 6 and tumour necrosis factor are the most important regulators of CRP synthesis. After stimulation with IL-6, IL-1 b, TNF and INF, the hepatocytes receive signals to start transcription of DNA coding for CRP. CRP begins to rise in bacterial infections within 4-6hours, peaks at 36-50hours, closely parallels acute response with 4-7 hour half-life, allowing to normal 3-7 days after the stimulus is withdrawn.

The classic triad of a history compatible with acute appendicitis, pain at McBurney's point and leucocytosis has diagnostic accuracy rate of less than 80 percent. And even when radiological techniques such as ultrasonography, computer tomography are included, the accuracy does not usually reach 90%. This is especially seen in females because of prevalence of pelvic inflammatory disease (PID) and other common obstetrical and gynaecological disorder and in the extremes of ages.

These factors resulted in relatively high rate of about 15-30% of negative explorations for acute appendicitis. And post operative morbidity associated with these negative explorations

is 5-15%. On one hand, a normal appendix at appendicectomy represents a misdiagnosis, on the other hand, a delayed diagnosis of appendicitis may lead to perforation and peritonitis.

So traditionally surgeons have accepted a higher incidence of unnecessary appendicectomies in order to decrease the incidence of perforations. This approach is being increasingly questioned in today's era of evidence based medicine. The high rate of negative explorations for appendicitis is a burden faced not only by the general surgeon, but also by the patient and the society as a whole, since appendicectomy like any other operation results in socioeconomic impact in the form of hospital expenses, lost working days and declining productivity. The goal of surgical treatment is removal of an inflamed appendix before perforation with a minimal number of negative appendicectomies.

To conclude as acute appendicitis may simulate many other acute abdominal conditions/illness and despite intensive clinical research and discussion, the diagnosis of acute appendicitis still remains a challenge. And the exact diagnosis is important for proper management.^[9,10]

C-reactive protein (CRP) together with other acute phase proteins, increases in response to tissue injury. Many reports have investigated the value of raised serum CRP measurement in improving the diagnosis of acute appendicitis.

In this study we correlate the serum levels of CRP with the histopathology of the removed appendix. This study emphasizes the impact of normal rather than raised serum C-reactive protein in reducing the rate of negative explorations.

MATERIALS & METHODS

In this double blind study patients coming to General Surgery Department of Govt Medical College Surypet who are diagnosed clinically as to have acute appendicitis form the source of study. They were included after explaining them about the study and taking their written consent.

Inclusion criteria:

All the patients who will be admitted to Govt Medical College & Hospital during the study period with diagnosis of acute appendicitis and posted for surgery are included in the study.

Exclusion criteria:

1. Children below 12 years and elderly above 50 years will be excluded as the CRP response is not optimal.
2. Patients who are managed conservatively are excluded from this study.
3. Patients with past history of jaundice, signs and symptoms of liver disease, chronic alcoholism are excluded as CRP is exclusively produced in liver.
4. Females taking oral contraceptive pill or pregnant are excluded as CRP is elevated in these individuals.

Method of collection of data:

Patient with history of acute abdominal pain were examined by a surgeon. For establishing the diagnosis, careful patient history was obtained at first. Physical examination of the patient by the surgeon was followed by some routine laboratory tests and radiographs.

In all the cases diagnosis was established by detecting right quadrant tenderness, guarding and rebound tenderness at physical examination. Thereafter it was decided by surgeon if emergency appendicectomy was necessary or not. Blood samples were drawn from all the patients who were diagnosed clinically as having acute appendicitis, for routine investigation as well as for CRP estimation. Serum CRP levels of all the patients were sent before operation which was done by latex agglutination method, normal value of serum CRP is 0.1 to 0.8 mg/dl, value above 2.5mg/dl, suggest an ongoing inflammatory process and were considered as positive. Patients with CRP levels <2.5mg/dl were considered as negative.

The results of measurement of CRP levels were not made available to the surgeons and were not taken into consideration for surgery, so as to compare diagnostic accuracy of CRP levels with surgeons clinical impression.

Appendix specimens were sent for histopathological examination to Department of Pathology, MMC&RI, operative findings and histopathological examination of appendectomy specimens established final and exact diagnosis.

Accordingly true and false surgeons clinical diagnosis, true and false positive or negative serum CRP results were determined. Based on these values specificity, sensitivity and accuracy of serum CRP concentrations were calculated.

Tests for C-reactive protein level estimation

CRP slide test for detection of CRP is based on the principle of agglutination. The test specimen (serum) is mixed with CRP latex reagent and allowed to react.

If CRP concentration is greater than 0.6mg/dl visible agglutination is observed. If CRP concentration is less than 0.6mg/dl, then no agglutination is observed. The latex slide test has the advantage of rapid performance in comparison to other tests for detection of CRP.

RESULTS

In our study 30 cases were included who were diagnosed as having acute appendicitis clinically by surgeons. They were told about the study and informed consent was taken.

Table 1: ?

Age in years	No. of patients	Percentage
0-10	-	-
11-20	5	16.66
21-30	10	33.33
31-40	9	30
41-50	6	20
>50	-	-

In present series age of patient varied from 12-50 years. Maximum number of patients were in age group 21-30 years i.e. 10 patients that forms about 33.33% of study group.

Table 2: Sex ratio

	No. of patients	Percentage
Male	12	40%
Female	18	60%

In 30 cases that were included in our study 18 were females, and 12 were males i.e. 60% of females and 40% of males were studied.

Table 3. Signs and symptoms

Signs & symptoms	No. of patients	Percentage
Abdominal pain	27	90%
Right iliac fossa Umbilical	6	20%
Vomiting	24	80%
Fever	15	50%
Diarrhoea	3	10%
McBurney tenderness	24	80%

Rebound tenderness	21	70%
Shifting tenderness	6	20%

All the patients in our study presented with pain abdomen i.e.100%. Most common site of pain being right iliac fossa (90%).

Fever as a presenting complaint was present in 15 patients (50%)

Vomiting as presenting complaint was seen in 80% of patients (24 study patients)

In 80% of patients McBurneys point tenderness noted. Rebound tenderness noted in 70% of patients. Shifting tenderness was noted in very few patients. Only 20% of patient showed shifting tenderness.

Table 4: Position of appendix

Position of appendix	No. of patients	Percentage
Retrocaecal	18	60%
Pelvic	6	20%
Paracaecal	3	10%
Sub-caecal	1	3.3%
Preilial	1	3.3%
Post ilial	1	3.3%

Per operatively most common position of appendix was found to be retrocaecal in 18 patients, which form 60% of our study patients.

It corresponds to the most common site of appendix anatomically. Next common position was pelvic and it formed 20% of total study cases. Other sites such as paracaecal, subcaecal, preilial, post ilial were found to be least common positions in our study.

Table 5: Histopathology results

Histopathology of appendix	No. of patients	Percentage
Normal histology	5	16.6%
Ac. Suppurative	15	50%
Ac.catarrhal	5	16.6%
Ac gangrenous	5	16.6%

In our study the appendix specimen was sent for histopathological examination to Department of Pathology, MMC&RI, Mysore. Out of 30 patients, 5 patients had normal histopathological picture of appendix so our negative appendicectomy rate was 16.6%.

Histopathologically 50% of patients had acute suppurative appendicitis. Remaining patients showed either acute catarrhal or acute gangrenous type of appendicitis.

Table 6: Correlation between CRP levels and histopathological findings

CRP level	CRP test				Total
	True		False		
	Positive	Negative	Positive	Negative	
Elevated	24	-	1	-	24
Normal	-	4	-	1	5
	28		2		30

In present series 24 patients had elevated serum CRP level (>2.5 mg/dl) which is 83.3% of total study group. In these patients only one patient had high serum CRP level inspite of

normal appendix that was proved histologically. The cause of raised serum level of CRP in this patient was mesenteric lymphadenitis which was found peroperatively.

Seven patients had normal serum CRP values i.e. 16.6% of patients. In these patients 4 83.3% had normal appendix on histopathological examination, whereas in 1 patient it was proved by histopathological examination that appendix was inflamed even though levels of CRP was normal in serum.

In our present study 95% of the CRP tests done are true whether level was raised or it was normal only 2(6.6%) of the tests done for CRP level estimation gave false report.

Test for C-Reactive Protein Level Estimation

Sensitivity $[(TP/TP+FN) \times 100]$	97.5%
Specificity $[(TN/TN+FP) \times 100]$	85%
Predictive accuracy of +ve test $[(TP/TP+FP) \times 100]$	96%
Predictive accuracy of -ve test $[(TN/TN+FN) \times 100]$	85%

TP=True positive TN=True negative FP= False positive FN=False negative

Sensitivity is the ability of the test to identify correctly all those who have the disease that is 'true positive'. Specificity is the ability of the test to identify correctly all those who do not have the disease that is 'true negative'.

In addition to sensitivity and specificity, the performance of a screening test is measured by its predictive accuracy, which reflects the diagnostic power of the test.

Predictive accuracy or value of positive test indicates the probability that a patient with a positive result has in fact the disease in question.

DISCUSSION

In study of "C-reactive protein as a diagnostic parameter in acute appendicitis – A double blind study", the diagnostic value of serum CRP levels in patients with clinically suspected acute appendicitis was investigated.

Emergency appendicectomy was done on patients with acute appendicitis based on clinical impression of the surgeon.

After the study it is noted that negative appendicectomy rate was 14%. This rate of negative appendicectomy was compared with other studies.

Table 7: Negative appendicectomy rates

Study done	Negative appendicectomy rate
Al-Saigh AR, ^[1]	14.3%
Albu E, ^[2]	10%
Thompson MM, ^[4]	8%
Our study	14%

In our study serum CRP level was elevated in 80% of the patients and this rate corresponds to study done by Albu et al where CRP levels were elevated in 85.7% of patients with acute appendicitis, also with study done by Thompson et al where 90% of patients had elevated CRP levels.

Serum CRP levels increases after the onset of inflammatory pathology, so the levels might be normal until about 12hrs after the onset of symptoms of acute appendicitis so the time interval between the appearance of symptoms and the actual testing of serum CRP levels had some bearing on the result shown by Al saigh et al and Asfar et al in their studies.

According to our study the sensitivity and specificity of serum levels in diagnosis of acute appendicitis is comparable to the results given by other researchers.

So it is derived from different studies that serum CRP test is highly sensitive and specific in making diagnosis of patients who truly had acute appendicitis.

In our study predictive accuracy of serum CRP estimation test for positive test is 93.3% and for negative test is 83.3%.

In our study surgeon's clinical diagnosis was correct in 25 patients i.e. in 83.3% of patients, whereas serum CRP estimation test was true in 28 patients that is 93.3% of patients.

This difference demonstrates the valuable contribution of preoperative serum CRP measurement to the clinical diagnosis of acute appendicitis.

According to our statistical analysis if we would have considered serum CRP level as a basis for deciding to perform appendicectomy, six unnecessary appendicectomies could have been avoided and we could have avoided much of morbidity and economic burden on patient and on our health system. Hence serum CRP estimation does not undermine the importance of clinical diagnosis of a skilled surgeon but complements it.

CONCLUSION

No doubt surgeon's clinical diagnosis using time tested clinical signs is effective in diagnosing acute appendicitis. However elevated serum CRP levels support the surgeon's diagnosis and hence avoids chances of error in diagnosis, due to atypical presentations. Similarly a normal preoperative serum CRP level in patients with suspected acute appendicitis is most likely to be associated with a normal appendix on histopathological examination. Therefore normal serum CRP level after 12 hours of onset of symptoms should be used as a basis for the decision to defer surgery to reduce the rate of negative appendicectomies, and also to reduce burden on patient as well as on health system.

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