

Role of serum C- reactive protein and leukocyte count in the diagnosis of acute appendicitis in Nepalese population

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ABSTRACT

Various diagnostic modalities have been reported to influence the negative appendectomy. C- reactive protein (CRP), an acute phase reactant, may improve the accuracy of diagnosing acute appendicitis. The present study was undertaken to evaluate the utility of CRP as a diagnostic tool among patients clinically suspected to have acute appendicitis. The role of total leukocyte (WBC) count was also studied. A total of 145 diagnosed cases of acute appendicitis were studied over a period of one and half years. CRP was raised in 91 cases and was normal in 54 cases. The sensitivity and specificity of CRP estimation in diagnosing appendicitis was 74.8% and 66.7% respectively and the sensitivity and specificity for total WBC count was 78.6 and 54.8% respectively. The present study suggests that we cannot rely wholly on CRP or on WBC count for operative decision. Clinical judgment is still the best modality for the diagnosis and operative management of acute appendicitis. It seems wiser to use active observation, which should identify most patients with non-specific pain and reserve operation for those who need it most.

Keywords: Serum C-reactive protein, leukocyte count, acute appendicitis.

INTRODUCTION

Appendicitis is the most common acute surgical condition of the abdomen.¹ Approximately 7.0% of the population will have appendicitis in their lifetime with the peak incidence occurring between the age of 10 and 30 years.² Abdominal pain is the most common clinical presentation.³ Anorexia, nausea and vomiting are other associated symptoms. The classical history of peri-umbilical pain at beginning and later shifting to right iliac fossa is present in only 50.0% cases. In 70.0% of the cases the clinical presentation is typical and there is no difficulty in making a diagnosis. The remaining 30.0% have atypical clinical presentation and present a diagnostic dilemma for the surgeons especially in the extreme of age, in women of reproductive age and with abnormal position of the appendix and thus have an uncertain preoperative diagnosis leading to unnecessary laparotomy and appendectomy.^{4,5} A negative appendectomy ranging from 10.0 to 44.0% has been considered acceptable by various authors with view to minimize the incidence of perforation and associated morbidity and mortality.⁶⁻⁹

Various diagnostic modalities have been reported to influence the negative appendectomy. This includes radiological, laparoscopy and laboratory methods of investigation. Leukocyte count has long been known to be a useful adjunct to the diagnosis of appendicitis; however, the utility of this test has been poorly characterized. A more recently suggested laboratory evaluation is determination of C-reactive protein level. C- reactive protein (CRP) is an acute phase reactant

synthesized by the liver in response to tissue injury. The measurement of CRP is available, easy to perform and very economical in comparison to radiological modalities and laparoscopy. As CRP is an inflammatory marker, it is expected to rise in case of acute appendicitis. Many workers have investigated the value of CRP in improving the diagnostic accuracy of acute appendicitis. A multivariate analysis showed that serial CRP measurement can improve the accuracy of diagnosing acute appendicitis,¹⁰ but other report did not support this view.¹¹ Therefore we carried out this study to evaluate the utility of CRP as a diagnostic tool among patients clinically suspected to have acute appendicitis.

MATERIALS AND METHODS

This study was conducted in the Department of Surgery, B. P. Koirala Institute of Health Sciences Dharan, over a period of 15 months. A total number of 145 cases with a clinical diagnosis of acute appendicitis were studied. A detailed clinical history and thorough clinical examination was done by the surgeon on duty. Relevant investigations like hemoglobin, leukocyte count, urine albumin, sugar and microscopic examinations were done in all cases. Blood sugar, blood urea, serum creatinine and plane X-ray abdomen were done only when needed. The final diagnosis of acute appendicitis was made clinically and supported by available laboratory investigation reports. Cases with the complication of appendicitis like appendicular lump, perforation and peritonitis were excluded from the study.

Blood sample for estimation of C-reactive protein (CRP)

was taken before operation. CRP was estimated by semi-quantitative method- Latex Fixation Slide Test (Rhelax CRP- Tulip Diagnostic, India).

The decision of operation was made independent of CRP level. The laboratory staffs were also not aware of the clinical findings, decision and the outcomes. Normal CRP level in our laboratory was < 6mg/dl and the level 6mg/dl and above was considered as raised for this study.

The operation was then performed and operative findings were noted. Appendix was removed and sent for histopathological examination. The findings of histopathological examination were based on following criteria:

1. Established acute inflammation: mucosal ulceration, transmural polymorph infiltrate, often with mural necrosis and serosal inflammatory response.
2. Normal: no evidence of acute inflammation.
3. Features suggestive of acute inflammation: focal true mucosal ulceration with polymorphs.
4. Peri-appendicitis: serosal, periappendicular inflammation with no evidence of any appendiceal mucosal/submucosal inflammation.

Statistics: The data was tabulated and analyzed the correlation between histopathology of appendix and serum CRP in terms of sensitivity and specificity in the Epi Info Program.

RESULTS

The study group included 70 females and 75 males. The age of the patients ranged from 6 years to 60 years (Table-1). Maximum numbers of patients 86 (59.2%) were from age group 11-30 years. Finally the correlation between the CRP results and histopathology reports was established. The correlation between histopathology of the appendix with serum CRP level is shown in Table-2. CRP was raised in 91 cases and normal in 54 cases. Appendicitis was diagnosed by histopathology in 103 cases and 42 cases had a normal appendix on histopathological examination. In the CRP raised group 77 cases had true appendicitis, and 14 cases had normal appendix on histopathological examination. Out of 103

Table-1: Age distribution of the patients

Age group in years	Number	Percent
1-10	7	4.8
11-20	49	33.7
21-30	37	25.5
31-40	27	18.6
41-50	16	11.3
51-60	9	6.2

Table-2: Correlation between histopathology of the appendix and serum C-reactive protein

Serum C-reactive Protein	Histological proved appendicitis	Histological proved normal appendix	Total
Raised	77 (TP)	14 (FP)	91
Normal	26 (FN)	28 (TN)	54
Total	103	42	145

TP: true positive; TN: true negative; FP: false positive; FN: false negative

cases of histopathologically proven appendicitis CRP was raised in 77 case and normal in 26 cases. Similarly among 42 cases where the appendix was histopathologically normal, CRP was raised in 14 cases and normal in 28 cases. Thus sensitivity and specificity of CRP estimation in diagnosing appendicitis was 74.8% and 66.7% respectively whereas the positive and negative predictive values were 84.9% and 51.9% respectively. Diagnostic accuracy of CRP was found to be 72.4% in this study.

Specificity = $TN \times 100.0\% / TN + FP = 66.7\%$

Sensitivity = $TP \times 100.0\% / TP + FN = 74.8\%$

Positive predictive value = 84.9%

Negative predictive value = 51.9%

Diagnostic accuracy = 72.4%

(TP: true positive; TN: true negative; FP: false positive; FN: false negative)

The correlation between histopathology of the appendix with WBC count is shown in Table-3. White blood cell count was raised ($> 11,000$ per mm^3) in 81 cases while the count was within normal limit in 22 cases of histopathological proven appendicitis group (103). In normal appendix group (42), 19 cases had raised WBC count and 23 cases had WBC count within normal limits. The sensitivity and specificity of WBC count was 78.6 and 54.8 percent respectively whereas the positive and negative predictive values were 81.0% and 51.1% respectively. Diagnostic accuracy of WBC estimation was found to be 71.7% in this study.

Specificity = $TN \times 100\% / TN + FP = 54.8\%$

Sensitivity = $TP \times 100\% / TP + FN = 78.6\%$

Positive predictive value = 81.0%

Negative predictive value = 51.1%

Diagnostic accuracy = 71.7%

We also analyzed the role of CRP and WBC combined

Table-3: Correlation between histopathology of the appendix and leukocyte count

Leukocyte count	Histological proved appendicitis	Histological proved normal appendix	Total
Raised	81 (TP)	19 (FP)	100
Normal	22(FN)	23 (TN)	45
Total	103	42	145

TP: true positive; TN: true negative; FP: false positive; FN: false negative

together in the diagnosis of appendicitis. Specificity and sensitivity was 40.5% and 91.3% whereas positive predictive value and negative predictive value were 79.0% and 65.4%. Diagnostic accuracy was increased to 76.6%.

DISCUSSION

The diagnosis of acute appendicitis is usually established on history, physical examination and leucocytosis.¹² The classical history of pain, beginning in the periumbilical region and shifting to right lower quadrant is found in 50.0% of the patients.¹ Many inflammatory and non-inflammatory conditions may mimic the presentation of acute appendicitis. This atypical presentation sometimes may result in diagnostic confusion and delay in treatment and thus increases the morbidity. Many prospective studies have demonstrated that the accuracy of preoperative clinical diagnosis lies in the range of mere 70.0-78.0% thus giving a negative appendicectomy rate around 20.0-25.0% on average.³ A negative appendicectomy ranging from 10.0-44.0 has been considered acceptable by various authors with a view to minimize the incidence of perforation and higher

mortality. Many vigorous attempts were made with various diagnostic modalities to reduce the negative laparotomy rate. The different modalities are based on radiological or other invasive procedures and laboratory tests to identify inflammatory markers.

Plain abdominal X-ray is rarely specific enough to be useful except for the demonstration of an appendicolith of 10.0% of adults and 50.0% of children. Barium enema provides a significant aid in equivocal instances, although findings are not totally specific for appendicitis. Ultrasonography (US) is appropriate in patients in whom the diagnosis is equivocal by history and physical examination. It is especially well suited evaluating right lower quadrant pain in pediatric and female patient.

Table-5: Diagnostic efficacy of leukocyte count

Authors	Specificity%	Sensitivity %	Count per Cmm ³
Marchand <i>et al</i> ²⁷	-	81	>10,000
Peltola ²⁸	-	58	>15,000
Ko <i>et al</i> ²⁴	65	85.2	>10,000
Agrawal <i>et al</i>	54.7	74.7	>11,000

Computed Tomography (CT) scan is more helpful in evaluating patient with suspected appendicitis.^{4,15} The negative appendicectomy rate fall from 20.0 before the use of CT to 7.0% after its introduction.¹⁶

Laparoscopy an invasive modality may be helpful in equivocal cases or in women of childbearing age group. It can be both diagnostic and therapeutic. But the rate of removal of normal appendix is also high with laparoscopy.¹⁷

The other modalities are laboratory investigation. Different authors have reported the diagnostic efficacy of leukocyte count and C-reactive protein. The white blood cell count is elevated (greater than 10,000 per mm³) in 80 percent of all cases of acute appendicitis.^{5,18,19} Unfortunately, the WBC is elevated in up to 70 percent of patients with other cause of right lower quadrant pain. Thus a serial elevated WBC measurement (over 4-8 hours) in suspected cases may increase the specificity, as the WBC count often increases in acute appendicitis (except in case of perforation, in which it may initially fall).¹⁹

There have been many reports emphasizing the value of CRP in improving the diagnostic accuracy of acute appendicitis. Multivariate analysis by Oosterhuis *et al* showed that serial CRP measurement could improve the accuracy of diagnosing acute appendicitis¹⁰. Other

Table-4: Diagnostic efficacy of serum C-reactive protein

Author	Specificity	Sensitivity	Cut off value of CRP (mg/dl)
Nordback and Harju ²¹	84.4	48.5	-
Sodenaa <i>et al</i> ²²	72	58	> 10 mg/dl
Al-Saigh ²³	76.3	39.7	-
Oosterhuis <i>et al</i> ¹⁰	50	87	> 6 mg/dl
Ko <i>et al</i> ²⁴	95	51	> 5 mg/dl
Gurleyik <i>et al</i> ²⁵	80	93.5	-
Asfar ¹²	86.6	93.6	-
Agrawal <i>et al</i>	66.7	74.8	> 6 mg/dl

reports did not support this view. In addition, a recent (1997) meta-analysis of 22 published articles concluded that CRP is a test of medium accuracy in diagnosing acute appendicitis.¹¹ Diagnostic efficacy of serum CRP of different study is shown in the Table-4. Diagnostic accuracy of CRP in our study was 72.4%.

In our study the CRP was estimated in 145 cases operated with clinical impression of acute appendicitis. The CRP was estimated by semi quantitative method with a cut off value of >6 mg/dl. CRP was raised in 91 cases and was normal in 54 cases. Appendicitis was diagnosed histopathologically in 103 cases but 42 cases had a normal appendix on histopathological examination. Among those patients whose CRP was raised there were 77 cases with histopathologically proved appendicitis, but 14 cases had a normal appendix removed. CRP was raised in 77 cases and was normal in 26 cases in histopathologically proved appendicitis group. Similarly CRP was raised in 14 cases and was normal in 28 cases in histopathologically normal appendix group and 26 cases had finding suggestive of appendicitis histopathologically and 28 cases had normal appendix removed among normal CRP group.

We had a negative appendectomy rate of 28.0% relying on clinical judgment, which is within the acceptable rate (10.0-44.0%).⁶⁻⁹ The sensitivity and specificity of CRP were found to be 74.8 and 66.7% respectively in our study, which matches to the group of authors mentioning CRP as a low predictor for diagnosing acute appendicitis,²²⁻²⁶ while relying solely on CRP, we could have prevented 28 negative appendectomies, and at the same time would have left 26 cases of acute appendicitis un-operated. Thus negative appendectomy would have fallen to 14.2%, but would have missed 17.8% of cases, which had true appendicitis.

Comparing the sensitivity and specificity of CRP with sensitivity and specificity of WBC count raised (11,000 per mm³) in 81 cases had WBC count within normal limit in histopathological proven appendicitis group, while 19 cases had WBC count raised and 23 cases had WBC count within normal in normal appendix group. Thus the sensitivity and specificity of WBC count was 78.6 and 54.8 percent respectively (Table-5), which is similar to the results of CRP test.

Natural course of appendicitis is not predictable. Different studies suggest that delay in presentation were responsible for the majority of perforated appendices. There is no accurate way of determining the time and commencement of appendix rupture prior to resolution of the inflammatory process. Although it has been suggested that observation and antibiotic therapy alone may be an appropriate treatment for acute appendicitis,

non-operative treatment risk the morbidity and mortality associated with a ruptured appendix. The overall mortality rate of perforated acute appendicitis is little higher than the rate for a general anesthetic, which is 0.06 percent. The overall mortality rate in ruptured acute appendicitis is about 3 percent - a 30 fold increased. The reported incidence of recurrent appendicitis in patients not undergoing interval appendectomy ranges from 0 to 37.0%.³ More recently research is going on the conservative approach in equivocal case. The concept of active observation has been put forward. Active observation is the management with nil per orally, intravenous fluids, sedation, regular nursing, urine and blood test, serial estimation of WBC and reassessment by same surgeon. The factors which promote perforation of an appendix includes extremes of age immunosuppression, diabetes mellitus, faecolith obstruction of the appendix lumen, a free lying pelvic appendix and previous abdominal surgery which limits the ability of the greater omentum to wall of the spread of peritoneal contamination. In these situations a rapidly deteriorating clinical course is accompanied by signs of diffuse peritonitis and systemic syndrome.²⁹

We can neither rely wholly on CRP nor on WBC count for operative decision. Clinical judgment is still the best modality for diagnosis of acute appendicitis and in judging whether operating management is required. It seems wiser to use active observation, which should identify most patients with non-specific pain and reserve operation for those who need it most.

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