

C-REACTIVE PROTEIN; A DIAGNOSTIC TOOL FOR ACUTE APPENDICITIS

Dr. Javaid Iqbal

FCPS

Associate Professor

Surgical Unit-I, Allied Hospital,
Punjab Medical College, Faisalabad

Dr. Farrukh Sami

Registrar

Surgical Unit-I, Allied Hospital,
Punjab Medical College, Faisalabad

Dr. Muhammad Afzal

FCPS

Senior Registrar

Surgical Unit-I, Allied Hospital,
Punjab Medical College, Faisalabad

Prof. Dr. A. G. Rehan

FCPS, FRCS

Surgical Unit-I, Allied Hospital,
Punjab Medical College, Faisalabad

ABSTRACT

OBJECTIVES: To determine the efficacy of C-reactive protein in diagnosis of acute appendicitis. **STUDY DESIGN:** Cross-Sectional Descriptive Study. **MATERIALS AND METHODS:** The study was conducted in Surgical Unit I of Allied Hospital, Faisalabad. The study was completed in six months, from 21 April 2005 to 30 June, 2005 and 26 January, 2006 to 26 May, 2006. In 100 patients with pain right iliac fossa, C-reactive protein, complete blood count and urine complete examination was done before appendectomy. Patients were assigned into group A (normal appendix) and group B (acute appendicitis) on the basis of histopathology. Normal TLC and CRP values, raised TLC, raised CRP level and raised both TLC and CRP values were calculated in these groups. Performance of C Reactive protein in comparison with histopathology (Gold Standard) was assessed. Results: In our study, 62 cases were males and 38 females. 83 cases had acute appendicitis and in 17 cases appendix was found to be normal. Patients having TLC >11,000 were 68 in group B and 03 in group A. Patients having TLC <11,000 were 15 in group B and 14 in group A. Patients having high CRP level were 77 in group B and 4 in group A. Patients having normal CRP level were 6 in group B and 13 in group A. The Specificity, Sensitivity, Predictive value (PV) of positive test, and Predictive value (PV) of negative test for CRP were 76.5%, 92.8%, 95.1% and 68.4% respectively. **CONCLUSION:** We found in this study that CRP was a good indicator of acute appendicitis and its routine use can decrease the rate of negative appendectomies.

KEY WORDS: C-reactive protein, Appendicitis Diagnosis of appendicitis, Total leukocyte count

CORRESPONDENCE: Dr. Javaid Iqbal, FCPS, Associate Professor, Surgical Unit-I, Allied Hospital, Punjab Medical College, Faisalabad. E-mail: apmcfds@gmail.com.

INTRODUCTION

The most common surgical procedure performed in emergency is appendectomy. Acute appendicitis develops in approximately 10% of the population in western countries¹. Acute appendicitis is mainly a disease of adolescents and young adults, but it may occur in any age group.

There are isolated reports of perityphlitis from the late 1500, recognition of acute appendicitis as a clinical entity is attributed to Reginald Fitz in 1886. Charles McBurney described the clinical

manifestations of acute appendicitis².

Appendix is a blind muscular tube (06-15cm) attached to the posteromedial surface of caecum approximately 3 cm infrolateral to the ileocecal junction³.

The position of appendix is variable being Retrocaecal in 74%, Pelvic 21%, Paracaecal 2%, Subcaecal 1.5%, Preileal and Postileal 0.5%². The usual pathologies of appendix are acute appendicitis, mucocele of the appendix, intussusception and tumors of appendix.

Appendiceal obstruction is the most common initial event of appendicitis. Hyperplasia of sub-mucosal lymphoid follicles account 60%, in older cases faecolith 35%¹.

Depending upon its position, sex and age of the patient, its presentation is different in different patients:

The diagnosis of acute appendicitis is mainly clinical which include symptoms (Periumbilical pain, Shifting of to right iliac fossa, Anorexia, Nausea), signs as (Pyrexia, Guarding, Tenderness and Rebound tenderness). Laboratory investigations like Plain X-ray abdomen, TLC, DLC, urine complete examination, USG and C.T help in the diagnosis¹. It has been estimated that the accuracy of the clinical diagnosis of acute appendicitis is 76% to 92%⁴. Despite improvements in diagnostic methods, negative appendectomy rates still remain 10-30% in acute appendicitis⁵.

There are certain acute phase-reaction proteins, which are raised in various inflammatory conditions. These proteins include C-reactive protein that was identified in 1930⁶. The C reactive protein is so named because it reacts as a precipitin with the C-polysaccharide of the pneumococcus, described originally as occurring in human serum in case of pneumonia.⁷

During an infection, microbial products such as endotoxin stimulate the release of IL-1, which is an endogenous pyrogen, and IL-6. These in turn act on liver to increase the synthesis and excretion of CRP⁸. Physiologically, CRP enhances cell-mediated immunity by promoting phagocytosis, accelerating chemotaxis, and activating platelets⁹.

Together with other acute phase-proteins, the serum level of CRP rises in response to any tissue injury. It also increases in response to infections (bacterial and viral) and also in non-infectious conditions like myocardial infarction, malignancies and rheumatic disorders¹⁰. So CRP monitoring makes a valuable contribution to the recognition and management of diseases like bacteremia and septicemia in children and adults, deep fungal infections, acute appendicitis, meningitis, infective relapse after abdominal surgery, burns, trauma and acute pancreatitis.¹¹

CRP can be studied with clinical data, lab investigations, and correlation with histopathology in the diagnosis of acute appendicitis¹².

If C-reactive protein can be added to the already existing laboratory tests, then the diagnosis of acute appendicitis with clinically suggestive signs can be made with fair degree of accuracy and as such unnecessary appendectomies can be avoided¹³. In this study we studied CRP along with clinical data, lab investigations, and correlated it with histopathology to diagnose the cases of acute appendicitis.

MATERIALS AND METHODS

STUDY DESIGN

Cross-Sectional Descriptive Study.

SETTING

The study was conducted in Surgical Unit-I of Allied Hospital, Faisalabad.

DURATION

The study was completed in six months, from 21 April 2005 to 30 June 2005 and 26 January 2006 to 26 May 2006.

SAMPLE SIZE

100 patients operated for acute appendicitis

SAMPLING TECHNIQUE

Convenience non-probability sampling

SAMPLE SELECTION

INCLUSION CRITERIA

1. With clinical suspicion of acute appendicitis
2. Age above 12 years. (<12 years are treated by pediatric surgery)

EXCLUSION CRITERIA

Right iliac fossa pain patients not treated with appendectomy

DATA COLLECTION PROCEDURE

An informed consent was obtained from all registered cases. In all the patients of pain right iliac fossa the provisional diagnosis of acute appendicitis was made on the basis of history, physical findings and relevant clinical data, CBC and urine C/E were done before appendectomy. Blood samples for the CRP measurements were collected just before

operation. Appendectomies were performed independent of the result of CRP levels. The laboratory staff was not aware of the clinical findings, decisions and outcome. Appendix specimens were sent for histopathological examination. All patients received perioperative antibiotics. Patients were divided in positive (acute appendicitis) and negative (normal appendix) groups on the basis of histopathology report.

The urine sample of the patients taken preoperatively were analyzed by strip method using Combure 10 of Roche. In the sample of blood taken preoperatively leukocyte count was determined by an electronic cell counter device (Medonic Cell Analyzer CA 620, Bovle Medical Stockholm, Sweden). The upper limit of reference values for TLC was 11000/mm³.

CRP was measured by dilution method using AVITEX CRP (latex agglutination test kit for detection of CRP) of Omega diagnostic UK. Normal CRP level in our laboratory is < 6 mg/dl. Levels above 6 mg/dl were considered as high. All the data of the patients was saved in the Performa (annexed).

DATA ANALYSIS PROCEDURE

For statistical purpose, these 100 patients were assigned into 2 groups, (A) Patients with normal appendix, (B) Patients with acute appendicitis. The number of patients with normal TLC and CRP values, raised total leukocyte count, raised CRP level and raised both TLC and CRP values were calculated in each of these groups. The data was entered into SPSS version 10.0 for descriptive analysis. P-value of <0.05 were considered to be statistically significant. A 2 x 2 table was used to assess performance of C Reactive protein in comparison with Histopathology (Gold Standard). Sensitivity, Specificity, Positive predictive value and Negative predictive value were determined by using formulas based on 2 x 2 table.

RESULTS

In this study, out of 100 patients, 62 (62%) cases were males and 38 (38%) females as shown in (Table No I).

In the male patients age range was 12 – 52 years with mean age 24 years and standard deviation (SD) 8.5. The highest numbers of patients (25) were in age group of 20-30 years (40.3%). As regard the

females, age ranged between 12 to 50 years with mean age 22.1 years and standard deviation (SD) 9.0, and the highest number of patients (17) were in age group 10 to 20 years (44.7%) as shown in (Table No: II).

Eighty-three (group B, 83%) cases had histopathological evidence of inflammation of the appendix, whereas in 17(group A, 17%) cases appendix was found to be normal. These were the cases of negative appendectomies (Table No: III).

Sixty-eight (81.9%) patients in group B (acute appendicitis) had TLC >11,000 while there were only 3 (17.7%) patients in group A having TLC >11,000. Patients having TLC <11,000 were 15 (18.1%) in group B and 14 (82.4%) in group A (Table No: IV).

The Specificity, Sensitivity, Predictive value (PV) of positive test, and Predictive value (PV) of negative test for TLC were 82.4%, 81.9%, 95.8% and 48.3% respectively

Regarding CRP values, in group A (normal appendix) 13 (76.5%) patients were having normal CRP level and 4 (23.5%) patients were having high CRP level. On the other hand in group B (acute appendicitis) 77 (92.8%) patients were having high CRP level and only 6(7.2%) patients were having normal CRP level ((Table No: V).

The Specificity, Sensitivity, Predictive value (PV) of positive test, and Predictive value (PV) of negative test for CRP were 76.5%, 92.8%, 95.1% and 68.4% respectively.

TABLE-I: SEX DISTRIBUTION

Sex	No of patients	Percentage
Male	62	62%
Female	38	38%

TABLE-II: DISTRIBUTION OF CASES BY HISTOPATHOLOGY Group A= Normal appendix Group B= Acute appendicitis

Histopathology of appendix	No of patients	Percentage
Negative (Group A)	17	17%
Positive (Group B)	83	83%
Total	100	100%

TABLE-III: FREQUENCY DISTRIBUTION OF AGE ACCORDING TO GENDER

Age in years	Male		Female	
	No of patients	Percentage	No of patients	Percentage
10-20	23	37.1%	17	44.7%
20-30	25	40.3%	14	36.8%
30-40	08	12.9%	04	10.5%
40-50	05	08.1%	02	05.3%
>50	01	01.6%	01	02.6%

TABLE-IV: TOTAL LEUKOCYTE COUNT IN GROUP A AND B

Group	TLC /mm ³ >11000	%	TLC /mm ³ <11000	%	No.
B(+ve)	68	81.9%	15	18.1%	83
A(-ve)	3	17.7%	14	82.4%	17
Total	71		29		100

Chi-Square = 34.77

P-value = 0.000

Specificity = $TN / (TN + FP) = 82.4\%$,

Sensitivity = $TP / (TP + FN) = 81.9\%$

Predictive value (PV) of positive test = $TP / (TP + FP) = 95.8\%$

Predictive value (PV) of negative

test = $TN / (TN + FN) = 48.3\%$

Diagnostic accuracy = $(TP + TN / \text{Total No}) \times 100 = 82\%$

KEY

(TP = true positive, TN = true negative, FP = false positive and FN = false negative, TLC = Total Leukocyte Count, Group A = Normal appendix, Group B = Acute appendicitis)

DISCUSSION

Acute appendicitis is mainly a disease of adolescents and young adults. Approximately 10% of the western population suffers from appendicitis¹. Appendectomy is the most common surgical procedure performed in an emergency. The diagnosis of acute appendicitis is mainly clinical and the accuracy of diagnosis is 76% to 92%⁴. Despite improvements in diagnostic methods, negative appendectomy rate still remain 10-30% in acute appendicitis⁵. Although the mortality of appendicitis

has declined, the overall morbidity from acute appendicitis occurs in 10% of the patients.¹⁴

To decrease the negative appendectomy rate, the clinical diagnosis of acute appendicitis should be supported by appropriate laboratory investigations. We designed this study to find out the efficacy of CRP in the diagnosis of acute appendicitis so that it can be added to the investigation tools for acute appendicitis.

C-reactive protein is an acute phase-protein, the serum level of which rises in response to any tissue injury. CRP level increases within 8 hours of the onset of tissue injury, peaks in 24-48 hours and remains high as long as there is continuing infection or tissue destruction¹⁵. CRP monitoring makes a valuable contribution to the recognition and management of diseases like acute appendicitis, acute pancreatitis, meningitis, deep fungal infections, burns and trauma¹¹.

In this study, 100 patients were included in which appendectomy was performed on the clinical grounds. The results of TLC and CRP were not made available to the operating team before the operation. Out of 100 patients, 17 (17% group A) were having histological proven normal appendix and 83 (83% group B) were having acute appendicitis. In group B 77 (92.8%) patients had increased CRP level as compared to TLC which was raised in 68 (81.9%) patients in the same group. On the other hand in group A 13 (76.5%) patients were having normal CRP and 14 (82.4%) patients were having TLC <11000/mm³. The sensitivity of CRP was 92.8% and the predictive value of positive test was 95.1%. We have found that in group B (acute appendicitis) both TLC and CRP values were high (82-93%). On the other hand in group A (normal appendix) CRP as well as TLC values were normal or lower (87-82%) in most of the patients. So if along with the clinical assessment of the patients with acute appendicitis the values of CRP and TLC would have been considered then the rate of negative explorations would have been decreased. It is suggested that if both CRP and TLC values are normal in an equivocal patient, then it is better to observe the patients and treat them conservatively. This policy will help the female patients in our setup as the Ultrasound facility is not available round the clock which is some-time essential to rule out other causes of right iliac fossa pain.

Asfar S, Safar H at Kuwait studied 78

patients in which appendectomy was performed. They found that CRP level were raised in histopathologically proven acute appendicitis. Serum CRP level was normal in 13 out of 15 negative explorations. The specificity and sensitivity of serum CRP was 86.6% and 93.6% respectively¹⁶. These findings were similar to our study

Gronroos JM and Gronroos P in Finland studied 100 consecutive patients retrospectively who underwent appendectomy on the clinical suspicion of acute appendicitis. The patients were divided in 3 groups, group A with uninflamed appendix, group B uncomplicated acute appendicitis and group C with complicated acute appendicitis. It was found that there was no patient in group B and C with both CRP and TLC values in the normal range¹⁷. So this study also matches to our results.

Gronroos JM also studied 83 consecutive elderly patients in which appendectomy was performed. He found that in 73 patients with acute appendicitis there was no one with both values unelevated¹⁸.

Erkasap S and his colleagues studied 102 patients in Turkey and found that the sensitivity and specificity of serum CRP were 96% and 87% respectively¹⁹. These findings were again in accordance with our study.

Faisal G Bhopal and his colleagues studied 150 patients in Sep 2000 to March 2001 in which appendectomy was performed on the clinical grounds. They found that the sensitivity and specificity of serum CRP were 98% and 87.5% respectively with a predictive value (PV) of positive test almost 98%¹³.

Jehangir S Khan studied 500 patients over a period of 3 years in which the incidence of negative appendectomy was 15% (75 cases). The sensitivity of TLC was 73% and specificity 80%. Likewise, the sensitivity of abdominal ultrasound was 86.2% and specificity 91.8%. CRP sensitivity was highest, 98.6% and specificity 88%. He suggest a combination of such investigations along with thorough physical examination is essential for accurate diagnosis of acute appendicitis²⁰.

Previous and present results suggest that CRP is of value in indicating acute pathology and its routine performance may decrease the negative appendectomy rate²¹. By decreasing the negative appendectomy rate, the burden on the public health system can be decreased.

CONCLUSION

We found in our study that CRP was a good indicator of acute appendicitis having sensitivity and specificity of serum CRP, 92.8% and 76.5% respectively with a predictive value (PV) of positive test almost 95% and that negative test in the range of 68.4%. So if C-reactive protein can be added to the already existing laboratory tests then the diagnosis of acute appendicitis can be made with a fair degree of accuracy and rate of negative appendectomies can be decreased.

REFERENCES

1. Finlay JD, Doherty MG. Acute abdominal pain and appendicitis. In: Doherty M D. The Washington manual of surgery. 3rd ed. Lipponcott William and Wilkins, 2002:257-67.
2. Connell PR. The vermiform appendix. In: Russel R, Williams NS, Bulstone CJ, Bailey and Love's Short practice of surgery. 23rd ed. London: Arnold, 2000:1077-78.
3. Steel C J. Disorder of small intestine and vermiform appendix. In: Cuschieri A. Essential surgical practice. 4th ed. London; Arnold, 2002:563-66.
4. Shakhathreh HS. The accuracy of C-reactive protein in the diagnosis of acute appendicitis compared with that of clinical diagnosis. Med Arh 2000;54:109-10.
5. Eryilmaz R, Sahin M, Alimoglu O, Bas G, Ozkan OV. The value of C-reactive protein and leukocyte count in preventing negative appendectomies. Ulus Travma Derg 2001;7:142-5.
6. Clyne B, Olshaker JS. The C-reactive protein. J Emerg Med 1999;17:1019-25.
7. Walter J B, Talbot I C. The plasma protein. In: Walter JB. Walter and Israel General Pathology. 7th ed. Churchill Livingstone, 1996:801-11.
8. Roitt M I. Innate immunity. Roitt MI, Delves JP. Roitt's Essential immunology. 10th ed. Blackwell Science, 2001:1-20.
9. Zimmerman MA, Selzman CH, Cothren C, Sorensen AC, Raeburn CD, Harken AH. Diagnostic implications of C-reactive protein. Arch Surg 2003;138:220-4.
10. Pepys MB, Baltz ML. Acute phase proteins with special reference to C-reactive protein and related

- proteins (pentraxins) and serum amyloid A protein. *Adv Immunol* 1983; 34: 141-212.
11. Pepys B M. The acute phase response and C-reactive protein. In: Warrell A D. *Oxford textbook of medicine*. 4th ed. Oxford University Press. 2003:150-56.
 12. Khan JS, Hassan H, Khan JA. Investigations for acute appendicitis: Can we rely on them?. *Pak J Surg* 2002;18:27-30.
 13. Bhopal FG, Ahmed BSH, Ahmaed M, Ahmed M, Khan JS, Mehmood N, et al. Role of TLC and C-reactive protein in the diagnosis of acute appendicitis. *J Surg Pak* 2003;8:14-7.
 14. Lewis FR, Holcroft JW, Boey J, Dunphy JE. Appendicitis: A critical review of diagnosis and treatment in 1000 cases. *Arch Surg* 1975;110:677-84.
 15. Young D.R. Results of Urgent Appendicectomy for Right Lower Quadrant Tenderness. *Am J Surg* 1989;157:428-30.
 16. Asfar S, Safar H, Khoursheed M, Dashti H. Would measurement of C-reactive protein reduce the rate of negative exploration for acute appendicitis?. *J R Coll Surg Edin*. 2000;45:21-4.
 17. Gronroos JM, Gronroos P. Leukocyte count and C-reactive protein in the diagnosis of acute appendicitis. *Br J Surg*. 1999;86:501-4.
 18. Gronroos JM. Is there a role for leukocyte and CRP measurements in the diagnosis of acute appendicitis in the elderly? *Maturitas*. 1999;31:255-58.
 19. Erkasap S, Ates E, Ustuner Z, Sahin A, Yilmaz S, Yasar B. Diagnostic value of interleukin-6 and C-reactive protein in acute appendicitis. *Swiss surg* 2000; 6:169-72.
 20. Jehangir S, Hassan H, Khan J A. Investigations for Acute Appendicitis: Can we rely on them? *Pak J Surg* 2002;18:27-30.
 21. Davies AH, Bernau F, Salisbury A, Souter RG. C-reactive protein in right iliac fossa pain. *J R Coll Surg Edinb* 1991;36:242-4.

**IF YOU ARE NOT PART OF THE
CURE, THEN YOU ARE PART OF THE
PROBLEM**