

SIGNIFICANCE OF C-REACTIVE PROTEIN LEVELS IN REDUCING NEGATIVE EXPLORATIONS FOR ACUTE APPENDICITIS

M. NAJMUDDIN SHABBIR,

Department of General Surgery, Fatima Jinnah Dental College, Karachi

ABSTRACT:

Objective: To study the significance of C-Reactive Protein in improving the diagnosis of acute appendicitis and to assess its role in preventing negative appendicectomies.

Design: Prospective, double blind study.

Setting: Sarfaraz Rafiquee Shaheed Hospital and Faiz-e-Aam Hospital, Karachi.

Patients: 100 consecutive patients with acute appendicitis who underwent surgery.

Methodology: Blood sample from 100 patients were collected pre-operatively for Total Leucocyte Count (TLC) and C-Reactive Protein (CRP). All specimen removed were sent for histopathology. The TLC, CRP and histopathology findings were correlated, and patients grouped into positive (acute appendicitis) and negative (normal appendix) cases.

Results: In patients with histopathologically proven acute appendicitis, both the TLC and CRP were significantly raised, $p=0.025$ and $p<0.0001$ respectively. However, in 16 out of 19 negative explorations (normal appendix on histopathology), serum CRP level was found to be normal. The specificity and sensitivity of serum CRP was 84.21% and 93.8% respectively.

Conclusion: A normal pre-operative serum CRP measurement in patients with suspected acute appendicitis is most likely associated with a normal appendix. Deferring surgery in this group of patients and/or further investigation into other possible causes might reduce the rate of unnecessary appendicectomies.

KEY WORDS: Acute appendicitis, Appendicectomy, Total Leucocyte Count, C-Reactive protein, Negative Exploration

INTRODUCTION

The diagnosis of acute appendicitis, a common surgical condition usually depends on the triad of clinical history, physical examination and leukocytosis. Atypical presentations are not uncommon, as many inflammatory and non-inflammatory conditions may mimic the presentation of acute appendicitis, especially in females and at extremes of age. These and other factors result in the relatively high rate (15-30%) of negative explorations for acute appendicitis¹⁻³. The reported post-operative morbidity associated with these negative explorations

is 5-15%^{1,3-6}. The situation creates the need for carrying out additional tests to improve diagnostic accuracy and reduce the unnecessary operations. This is especially important today, when cost containment drives health planning.

CRP, together with other acute-phase proteins, increases in response to tissue injury⁷. Many reports have investigated the value of raised serum CRP measurement in improving the diagnosis of acute appendicitis.

In this study, the serum levels of CRP were correlated with TLC and the histopathology of the removed appendix. The question as to whether a normal CRP value would exclude the presence of acute appendicitis was also addressed.

PATIENTS & METHODS

This study was conducted on one hundred consecutive patients of acute appendicitis who were admitted and

Correspondence :

Dr. M. Najmuddin Shabbir, Associate Professor,
Department of General Surgery.

Fatima Jinnah Dental College, Karachi.

Phones: 0300-8229833

E-mail: drnajamshabbir@hotmail.com

operated at Sarfaraz Rafiquee Shaheed Hospital and Faiz-e-Aam Hospital, Karachi. Pre-operative blood samples for TLC and CRP measurement were collected from all these patients. The decision to operate was made independent of the CRP level, as the result was not available to the surgical team during the hospital stay of these patients. The laboratory staff was also not aware of the clinical findings, decisions and outcomes (double blind study).

The criteria used for the diagnosis of acute appendicitis included:

- history of abdominal pain localized to the right iliac fossa or lower abdomen.
- clinical findings of shifting pain.
- clinical findings of tenderness, guarding and/or rigidity in the right iliac fossa or lower abdomen.
- leukocytosis of more than $10 \times 10^9/\text{dl}$.

The mean age of the patients was 25.5 ± 10.8 (range 8-45) years. There were 69 males and 31 females. All the patients presented within 24-36 hours of the onset of pain. The removed appendices from all the 100 patients were sent for histopathological examination. The results were then used to categorize the operations as positive (acute appendicitis) or negative (normal appendix). The white blood count (WBC), CRP level and histopathology findings were compared to assess the impact of serum CRP measurements on the diagnosis of acute appendicitis.

Quantitative serum CRP was measured by the nephelometer (Array protein chemistry system, Beckman instruments, Fullerton, CA, USA). CRP level of 0-0.8 mg/dl was considered normal whereas levels above 2.0 mg/dl were considered as high. The results were analyzed by using one-way ANOVA for multiple comparisons. The differences between the two groups were determined by paired student t-test using Statview-4.02 statistics package, p-value of <0.05 was considered significant.

RESULTS

Table I shows the correlation between the histopathology

Table I. Co-relation between Histopathology Serum CRP level and TLC

Other Variable	-ve Histopathology (n=19)	+ve Histopathology (n=81)	P-value
WBC ($\times 10^9/\text{dl}$)*	10.0 ± 3.05	13.68 ± 6.07	0.025
CRP (mgm/dl)*	1.84 ± 1.23	6.47 ± 3.43	<0.01

of the removed appendix, TLC and the serum CRP levels. In patients with proven acute appendicitis (+ve) on histopathology, both the WBC and CRP levels were found to be significantly high ($p=0.025$ and $p<0.0001$, respectively) when compared with that of patients with normal appendices (negative). The mean CRP level in patients with positive exploration was 6.47 ± 3.43 mgm/dl and 1.8 ± 1.32 mgm/dl in patients with normal appendix. Only three patients in the later group had a high CRP level (Table II). These include two females, aged 22 and 25 years, who had ruptured ovarian cysts (CRP=2.5 and 3.5 mgm/dl respectively) and a 32 year old male who had acute terminal ileitis (CRP=6 mgm/dl).

Serum CRP measurement was highly sensitive and highly specific (Table III), with high predictive value in patients with acute appendicitis as follows:

Specificity	$\text{TN}/\text{TN} + \text{FP} = 16/16+3 = 84.2\%$
Sensitivity	$\text{TP}/\text{TP} + \text{FN} = 76/76+5 = 93.8\%$
Predictive value	
Specificity	$\text{TP}/\text{TP} + \text{FP} = 76/76+3 = 93.2\%$
Sensitivity	$\text{TN}/\text{TN} + \text{FN} = 16/16+5 = 76.1\%$

(FP=false positive, TP=true positive, FN=false negative
TN=true negative)

DISCUSSION

CRP was first found in the serum of patients suffering from pneumonia caused by *Streptococcus pneumoniae*⁸. 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 in non-infectious conditions like myocardial infarction, malignancies and rheumatic disorders⁷. CRP concentration 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 destruction^{9,10}. Due to its short half-life (4-7 hours) serum CRP concentration rapidly declines as the acute inflammatory process subsides¹¹. Many reports have investigated the value of CRP in improving the diagnostic accuracy of acute appendicitis with conflicting results. A multi-variate analysis by Oosterhuis et al¹² showed that serial

Case	Sex	Age (years)	TLC -10 ⁹ /dl	CRP Mgm/dl	Final diagnosis
1.	F	22	11	2.5	Ruptured ovarian cyst
2.	F	25	13	3.5	Ruptured ovarian cyst
3.	M	32	8	6.0	Terminal ileitis
4.	F	17	8	1.0	Ovarian cyst
5.	F	27	6	1.0	Ovarian cyst
6.	F	29	8	1.0	Ovarian cyst
7.	F	35	11	1.0	Ovarian cyst
8.	F	36	18	2.0	Pelvic inflammatory disease
9.	F	35	13	1.0	Non-specific abdominal pain
10.	F	23	14	1.0	Non-specific abdominal pain
11.	F	52	6	1.0	Non-specific abdominal pain
12.	M	30	12	2.0	Non-specific abdominal pain
13.	M	27	11	2.0	Non-specific abdominal pain
14.	M	16	10	1.0	Non-specific abdominal pain
15.	M	43	12	1.0	Non-specific abdominal pain
16.	M	41	10	2.0	Non-specific abdominal pain
17.	M	25	11	2.0	Non-specific abdominal pain
18.	M	13	8	2.0	Non-specific abdominal pain
19.	M	14	10	2.0	Non-specific abdominal pain

Table II. Details of 19 patients who had negative explorations for acute appendicitis

CRP measurement can improve the accuracy of diagnosing acute appendicitis. Other reports did not support this view¹³. In addition, a recent (1997) meta-analysis of 22 published articles concluded that CRP is a test of medium accuracy in diagnosing acute appendicitis¹⁴.

In this study, in all patients who had histologically proven acute appendicitis, both the pre-operative TLC and the serum CRP were significantly high ($p=0.025$ and $p<0.0001$ respectively). The rate of negative explorations for appendicitis was 19% ($n=19$) which is in accord with previous series¹⁻³. In this group of patients, the pre-operative CRP levels were found to be normal

in all but three patients. The latter had other intra-abdominal pathologies causing the rise in CRP. These results would suggest that a normal pre-operative serum CRP level is not associated with acute appendicitis.

These findings are in accord with a recent retrospective study which showed no rise in the pre-operative TLC or CRP level in all patients in whom the removed appendix was normal (24%). The authors concluded that appendicectomy is not recommended when the TLC and CRP were normally preoperatively¹⁵.

In 1994, Erikson et al¹⁶, in a cohort of 227 patients with

Table III. The Specificity, Sensitivity and the Predictive values of Serum CRP Measurement in the Diagnosis of acute Appendicitis (FP=False +ve, TP=True +ve, TN=True -ve, FN=False -ve)

CRP level	-ve Histopathology	+ve Histopathology	Total
High	3 (Fp)	76 (Tp)	79
Normal	16 (Tn)	5 (Fn)	21
Total	19	81	100

suspected acute appendicitis measured serum CRP levels and TLC counts every four hours and reported that it was unusual to find a normal CRP level after 8 hours of observation in the presence of acute appendicitis. Moreover, in a double-blind prospective trial Albu et al¹⁷ studied 56 patients and, as with this study, the results of CRP levels were not made available to the surgeon during the patients' hospital stay. They concluded that a normal CRP level (<2.5 mg/dl), 12 hours after the onset of symptoms excluded the diagnosis of acute appendicitis. The high positive and negative predictive values (96.7% and 76.5%, respectively) of serum CRP reported in the current study are in complete accord with these reports.

CONCLUSION

The data presented in this study and the current literature would suggest that normal pre-operative CRP levels are not likely to be associated with acute appendicitis. Deferring emergency appendectomy in this group of patients would probably reduce the rate of unnecessary appendectomies. Further prospective studies are required to verify the validity of such a proposition.

REFERENCES

1. Jess P, Bjerregaard B, Brynitz S, Hoist Christensen J, Kalaja E, Lund Kristensen J. Acute appendicitis: prospective trial concerning diagnostic accuracy and complications. *Am J Surg* 1981; 141: 232-234.
2. Pieper R, Kager L, Nasman P. Acute appendicitis: a clinical study of 1018 cases of emergency appendectomies. *Acta Chir Scand* 1982; 148: 51-62.
3. Hoffmann J, Rasmussen O. Aids in the diagnosis of acute appendicitis. *Br J Surg* 1989; 76: 774-9.
4. Mason LB, Deyden WE. Primary appendectomy. *Am J Surg* 1976; 42: 239-43.
5. Lewis FR, Holcroft JW, Boey J, Dunphy JE. Appendicitis: a critical review of diagnosis and treatment in 1000 cases. *Arch Surg* 1975; 110: 667-684.
6. Change FC, Hogle HH, Welling DR. The fate of the negative appendix. *Am J Surg* 1973; 126: 752.
7. Pepys MB. C-reactive protein fifty years on. *Lancet* 1981; 1: 653-656.
8. Tillet WS, Francis T. Serological reactions in pneumonia with a non-protein somatic fraction of pneumococcus. *J Exp Med* 1930; 52: 561-571.
9. Young B, Gleeson M, Cripps A. C-reactive protein: a critical review. *Pathology* 1991; 23: 118-124.
10. Kragstbjerg P, Holmberg H, Vikerfors T. Serum concentrations of interleukin-6, tumour necrosis factor and C-reactive protein in patients undergoing major operations. *Eur J Surg* 1995; 161: 17-22.
11. Pepys MB, Baltz ML. Acute phase proteins with special reference to C-reactive protein and related proteins (pentaxins) and serum amyloid A protein. *Adv Immunol* 1983; 34: 141-211.
12. Oosterhuis WP, Zwinderman AH, Teeuwen M, VanAndel G, Oldenzil H, Kerckhoff IF, Siebbeles HW, VanDer Helm HI. C-reactive protein in the diagnosis of acute appendicitis. *Eur J Surg* 1993; 159: 115-119.
13. Thompson MM, Underwood MI, Dookeran KA, Lloyd DM, Bell PR. Role of sequential leucocyte counts and C-reactive protein measurements in acute appendicitis. *Br J Surg* 1992; 79: 822-4.
14. Hallan S, Asberg A. The accuracy of C-reactive protein in diagnosing acute appendicitis - a meta analysis. *Scand J Clin Lab Invest* 1997; 57: 373-380.
15. Gronroos JM, Gronroos P. Leucocyte count and C-reactive protein in the diagnosis of acute appendicitis. *Br J Surg* 1999; 86: 501-504.
16. Eriksson S, Granstrom L, Carstrom A. The diagnostic value of repetitive pre-operative analyses of C-reactive protein and total leucocyte count in patients with suspected acute appendicitis. *Scand J Gastro Enterol* 1994; 29: 1145-1149.
17. Albu E, Miller BM, Choi Y, Lakhanpal S, Murthy RN, Gerst PH. Diagnostic value of C-reactive protein in acute appendicitis. *Dis Colon Rectum* 1994; 37: 49-51.