C-REACTIVE PROTEIN; A DIAGNOSTIC TOOL FOR ACUTE APPENDICITIS

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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 appendicectomies.

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

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INTRODUCTION

The most common surgical procedure performed in emergency is appendicectomy. Acute appendicitis develops in approximately 10% of the population in western countries\(^1\). Acute appendicitis is mainly a disease of adolescents and young adults, but it may occur in any age group.

There are isolated reports of perityphilitis 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 appendicitis\(^2\).

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

The position of appendix is variable being Retrocaecal in 74%. Pelvic 21%, Paracaecal 2%, Subacaecal 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%. 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 diagnosis. It has been estimated that the accuracy of the clinical diagnosis of acute appendicitis is 76% to 92%. Despite improvements in diagnostic methods, negative appendectomy rates still remain 10-30% in acute appendicitis.

There are certain acute phase-reaction proteins, which are raised in various inflammatory conditions. These proteins include C-reactive protein that was identified in 1930. 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.

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 CRP. Physiologically, CRP enhances cell-mediated immunity by promoting phagocytosis, accelerating chemotaxis, and activating platelets.

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 disorders. So CRP monitoring makes a valuable contribution to the recognition and management of diseases like bacteremia and sepsis in children and adults, deep fungal infections, acute appendicitis, meningitis, infective relapse after abdominal surgery, burns, trauma and acute pancreatitis.

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

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 avoided. 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

A.P.M.C Vol: 1 No.1 January 2007
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 leucocyte 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 11,000/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 leucocyte 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**

<table>
<thead>
<tr>
<th>Sex</th>
<th>No of patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>62</td>
<td>62%</td>
</tr>
<tr>
<td>Female</td>
<td>38</td>
<td>38%</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Histopathology of appendix</th>
<th>No of patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative (Group A)</td>
<td>17</td>
<td>17%</td>
</tr>
<tr>
<td>Positive (Group B)</td>
<td>83</td>
<td>83%</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>100%</td>
</tr>
</tbody>
</table>
TABLE-III: FREQUENCY DISTRIBUTION OF AGE ACCORDING TO GENDER

<table>
<thead>
<tr>
<th>Age in years</th>
<th>Male</th>
<th>Male Percentage</th>
<th>Female No. Of Patients</th>
<th>Female Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-20</td>
<td>23</td>
<td>37.1%</td>
<td>17</td>
<td>44.7%</td>
</tr>
<tr>
<td>20-30</td>
<td>25</td>
<td>40.3%</td>
<td>14</td>
<td>36.8%</td>
</tr>
<tr>
<td>20-40</td>
<td>08</td>
<td>12.9%</td>
<td>04</td>
<td>10.5%</td>
</tr>
<tr>
<td>40-50</td>
<td>05</td>
<td>08.1%</td>
<td>02</td>
<td>05.3%</td>
</tr>
<tr>
<td>&gt;50</td>
<td>01</td>
<td>01.6%</td>
<td>01</td>
<td>02.6%</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Group</th>
<th>TLC /mm3</th>
<th>%</th>
<th>TLC /mm3 &lt;11000</th>
<th>%</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>B(+)ve</td>
<td>68</td>
<td>81.9%</td>
<td>15</td>
<td>18.1%</td>
<td>83</td>
</tr>
<tr>
<td>A(+)ve</td>
<td>3</td>
<td>17.7%</td>
<td>14</td>
<td>82.4%</td>
<td>17</td>
</tr>
<tr>
<td>Total</td>
<td>71</td>
<td>17.7%</td>
<td>29</td>
<td>82.4%</td>
<td>100</td>
</tr>
</tbody>
</table>

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/Total No.) X 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 appendicitis. Appendicectomy 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%. Despite improvements in diagnostic methods, negative appendicectomy rate still remain 10-30% in acute appendicitis. Although the mortality of appendicitis has declined, the overall morbidity from acute appendicitis occurs in 10% of the patients.

To decrease the negative appendicectomy 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 destruction. CRP monitoring makes a valuable contribution to the recognition and management of diseases like acute appendicitis, acute pancreatitis, meningitis, deep fungal infections, burns and trauma.

In this study, 100 patients were included in which appendicectomy 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 appendicectomy 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% respectively. These findings were similar to our study.

Grouroos JM and Grouroos P in Finland studied 100 consecutive patients retrospectively who underwent appendicectomy on the clinical suspicious 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 range. So this study also matches to our results.

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

Erbasap S and his colleagues studied 102 patients in Turkey and found that the sensitivity and specificity of serum CRP were 96% and 87% respectively. 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 appendicectomy 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%.

Jehangir S Khan studied 500 patients over a period of 3 years in which the incidence of negative appendicectomy 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 appendicitis.

Previous and present results suggest that CRP is of value in indicating acute pathology and its routine performance may decrease the negative appendicectomy rate. By decreasing the negative appendicectomy 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 appendicectomies can be decreased.

REFERENCES

10. Pepys MB, Baltz ML. Acute phase proteins with special reference to C-reactive protein and related

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