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Research Article

PREDICTIVE VALUE OF INFLAMMATORY MARKERS IN ACUTE APPENDICITIS AND THEIR COMPLICATIONS

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ABSTRACT
Acute appendicitis is one of the most common acute intra abdominal infections seen in surgical departments, which can be treated early and easily if an accurate diagnosis is made in time. The aim of this study is to determine the diagnostic value of serum inflammatory markers in patients with suspected diagnosis of acute appendicitis. To find out the correlation between the level of inflammatory markers and complications. This is a prospective study conducted at the Department of General Surgery at St. Isabel Hospital, Chennai from 1st October 2012 to 28th February 2014. 55 patients who underwent appendicectomy for acute appendicitis were categorized as 3 groups as per histology report and intra-operative findings. Group 1- undetermined group which included chronic appendicitis, lymphoid hyperplasia, and chronic obliterative appendicitis. Group 2- inflamed appendicitis without any complications. Group 3- complicated appendicitis which included perforation, abscess, and necrosis. Group 2 and Group 3 were together considered as acute appendicitis in the present study. The association of outcome parameters in two study groups with and without complications and among groups of appendicitis was assessed by calculating Mean, Mean difference and their 95% CI and p-value by Independent T-test or Paired T-test and One way ANOVA analysis. It shows that there is statistical significance associated with WBC (p value=0.044) and CRP (p value=0.001) whereas IL-6 (p value=0.12), IL-8(p value=0.466), TNF-A (p value=0.26) has no significance. Novel inflammatory markers like IL-6, IL-8, TNF-A have been introduced off late and have a future application to predict acute inflammation and to decide on surgery prior to complication and also decrease unnecessary appendicectomies but they are expensive for day to day practice though of a good academic value

Keywords: *Acute Appendicitis, Inflammatory Markers, Appendicectomy*

INTRODUCTION
Appendicitis is an inflammation of appendix which may follow obstruction to the lumen of appendix. It causes increased intra luminal pressure and retention of contents which allows suppuration to occur. Acute appendicitis is one of the most common acute intra abdominal infections seen in surgical departments, which can be treated early and easily if an accurate diagnosis is made in time. Overall lifetime risk for appendicectomy is 7%. The lifetime risk of negative appendectomy rate is 12% for men and 29% for women (Goodwin *et al.,* 1997). If all ages are considered mortality rate is around 0.25% (Ergul *et al.,* 2008). Cases of missed appendicitis result in complications such as appendiceal perforation or abscess formation.

Patients at extremes of age are more likely to develop complications like perforated appendicitis and peritonitis. Appendicitis is more common in adolescents and young adults (Ergul *et al.,* 2008). A typical patient is one presenting with right lower abdominal pain, nausea and vomiting. On examination patient will have tenderness and guarding in right iliac fossa. However, these signs and symptoms are not very specific for appendicitis and can mimic in other acute abdominal conditions also.

Despite advances in diagnostic modalities, the diagnosis is still doubtful in 30-40 % of cases and the definite diagnosis of appendicitis still remains a clinical decision, augmented by appropriate tests. A high degree of diagnostic accuracy is required to reduce the incidence of negative appendicectomy which still remains around 20 % (Goodwin *et al.,* 1997; Kaya *et al.,* 2012). The wide range of causes and varied presentation poses a formidable diagnostic and therapeutic dispute. Appendicectomy for appendicitis is

the most commonly performed emergency operation in the world. The accuracy of diagnosis can be increased by investigatory modalities like Ultrasonogram, Computed tomogram, Magnetic resonance imaging and Diagnostic laparoscopy (Gaitini *et al.,* 2008). Despite the increased use of ultrasonography, computed tomographic scanning, and laparoscopy, the rate of misdiagnosis of appendicitis has remained constant, as has the rate of appendiceal rupture. The percentage of misdiagnosed cases of appendicitis is significantly higher among women than men. This is a burden not just on the surgeon but also on patient, hospital and whole community. This result in increased hospital expenses, loss of working days, decreased productivity, impact on economic status. An over diagnosis might result in negative exploration, whereas delayed diagnosis may cause complications such as perforation and abscess formation (Vinoth *et al.,* 2011). In view of this, various clinical and laboratory tests have been tried to diagnose acute appendicitis and their complications at an early stage. Studies have shown inconsistent information regarding the use of WBCs count in diagnosis of acute appendicitis. Many of the acute inflammatory markers are increased in the body during appendicitis. Unfortunately, no marker has been found to show significant promise for the diagnosis of acute appendicitis mainly because of the high cost involved and low accuracy. Immune responses and inflammatory factors are important for inflammatory conditions in the appendix. Immune responses and cytokine patterns could determine an outcome of appendicitis (Daneshmandi *et al.,* 2009). Cytokines is a group of proteins which are produced to mediate and regulate the inflammatory and immune response (Yoon *et al.,* 2002). Higher levels of interleukin-6 and 8 are associated with perforated appendix (Dzabic *et al.,* 2008). This study is to determine whether WBC counts, CRP, IL-6, IL-8, and TNF-α can help in predicting acute appendicitis and their correlation in complications of appendicitis.

MATERIALS AND METHODS

Study Type: This is a prospective experimental study.

Inclusion Criteria

All adult patients clinically suspected to have acute appendicitis. Those with radiological evidence of acute appendicitis were taken into the study. Patients who are undergoing surgery at our institution.

Exclusion Criteria

Patients presenting with abdominal pain and having other inflammatory condition like Mesenteric adenitis, ulcerative colitis, crohn's disease, pelvic inflammatory disease, ruptured ovarian cyst, ectopic pregnancy, and diverticulitis. Paediatric patients are not included. Radiological diagnosis of other pathology. Patients managed on medical therapy were excluded. Patients who declined to participate in this study.

Limitations

During the period of study of 18 months, only 55 samples could be collected as the tests were expensive. Present study was analyzed with mean value of markers. No clear cut off value to suggest inflammation and degree of inflammation are available as each laboratory has arbitrary values. Due to technical reasons, samples were analyzed once in 2-3 months after collecting adequate number of samples, till then samples were preserved in deep freeze.

Serial estimation of inflammatory markers prior and after the intervention would have given more information about the inflammatory markers. Observational error in CRP and WBC may be possible as some samples were done in different laboratories.

Aims of this Study

1- To determine the diagnostic value of serum inflammatory markers in patients with suspected diagnosis of acute appendicitis.

2- To find out the correlation between the level of inflammatory markers and complications.

Study Sample Characteristics

Patients who were found to satisfy the entry criteria were included in this study. A well informed consent was obtained prior to the surgery. The study was done from 1st October of 2012 till 28th of February 2014.

55 patients of suspected case of acute appendicitis who underwent surgery in our hospital above the age of 14yrs were included in the study.
On admission clinical symptoms and signs were recorded. Symptoms like pain, fever, vomiting were recorded. Signs included tenderness in the right lower abdomen, guarding and rebound tenderness were recorded.

Figure 1: Automated WBC reader

Normal CRP level in our laboratory was measured by nephelometry.

Figure 2: Automated CRP reader

IL-6, IL-8, TNF-α levels were measured with sandwich enzyme linked
Immunosorbent assay (ELISA). A standard curve was constructed. Each serum sample was measured in duplicate.

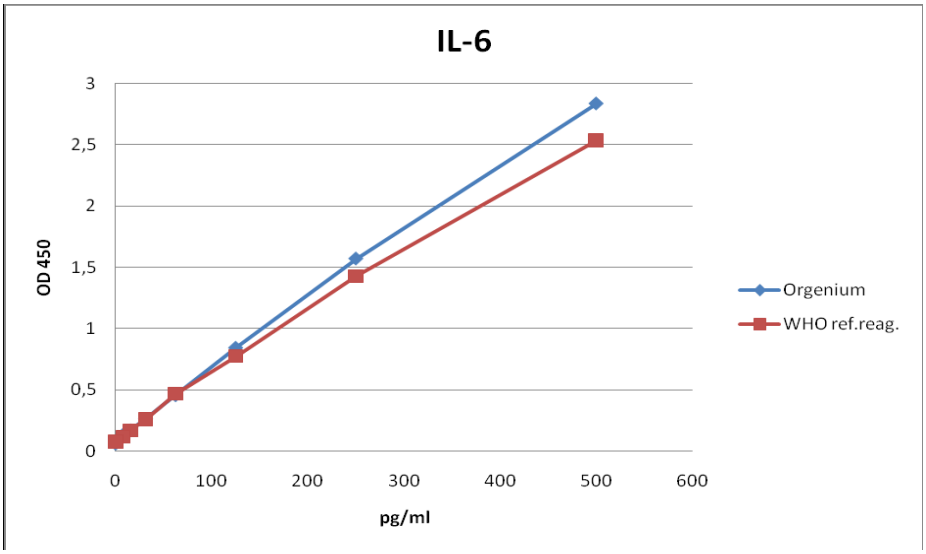

Figure 3: WHO standard curve of IL-6

RESULTS AND DISCUSSION

Results

This is a prospective study conducted at the Department of General Surgery at St. Isabel Hospital, Chennai from 1st October 2012 to 28th February 2014. 55 patients who underwent appendicectomy for acute appendicitis were categorized as 3 groups as per histology report and intra-operative findings. Group 1- undetermined group which included chronic appendicitis, lymphoid hyperplasia, and chronic obliterative appendicitis. Group 2- inflamed appendicitis without any complications. Group 3- complicated appendicitis which included perforation, abscess, and necrosis. Group 2 and Group 3 were together considered as acute appendicitis in the present study.

The Range of Various Markers in the Present Study Group

Table 1: The range of CRP in mg/dl

<50	50-100	100-150	150-200	200-250	>250
31	8	5	5	2	3

This table shows that 31 among 55 patients had a CRP value below 50 and the rest above.

Table 2: The Range of IL-6 in pg/dl

<40	40-80	80-120	120-160	160-200
32	17	2	3	1

This table shows that 32 among 55 patients had an IL-6 levels below 40 and the rest above.

Table 3: The Range of IL-8 in pg/dl

<40	40-80	80-120	>120
47	4	3	1

This table shows that 47 patients had IL-8 value less than 40 and the rest above.

Table 4: The Range of TNF-A in pg/dl

<40	40-80	80-120	>120
47	5	2	1

This table shows that 47 among 55 patients had TNF-A value less than 40 and the rest above.

Table 5: Association of all inflammatory markers in various groups

Parameter	Impressions	Mean	F- Statistic	p-value
WBC	Undetermined	10469.231	3.321	.044
	inflamed	12552.000		
	Complicated	14035.294		
	Undetermined	36.338	8.165	.001
CRP	inflamed	56.804		
	Complicated	147.371		
	Undetermined	25.8215	2.206	.120
IL6	inflamed	50.2504		
	Complicated	52.5012		
	Undetermined	19.692	.775	.466
IL8	inflamed	26.600		
	Complicated	32.353		
	Undetermined	14.4038	1.381	.260
TNF Alpha	inflamed	29.4800		
	Complicated	36.4118		

This table shows association of inflammatory markers in all 3 groups. It shows that there is statistical significance associated with WBC (p value=0.044) and CRP (p value=0.001) whereas IL-6 (p value=0.12), IL-8(p value=0.466), TNF-A (p value=0.26) has no significance.

Table 6: Inflammatory markers in relation to acute appendicitis versus undetermined.

Groups	Mean	Mean difference	P value	95% CI Lower
I. WBC				
Acute appendicitis	13152.381	2683.1502	.029	278.6658
Undetermined	10469.231			
II. CRP				
Acute appendicitis	93.462	57.1234	.056	-1.5628
Undetermined	36.338			
III.IL6				
Acute appendicitis	51.1614	25.33989	.039	1.26898
Undetermined	25.8215			
IV. IL8				
Acute appendicitis	28.929	9.2363	.294	-8.2456
Undetermined	19.692			
V.TNF Alpha				
Acute appendicitis	32.2857	17.88187	.125	-5.15258
Undetermined	14.4038			

This table shows comparison of inflammatory markers in acute appendicitis (group 2 +group 3) with the undetermined group (group 1). WBC (p value= 0.029) and IL-6 (p value=0.039) has positive correlation while CRP (p value= 0.056), IL-8 (p value=0.29), TNF-A (p value= 0.12) had no positive correlation.

Discussion

Acute appendicitis is one of the common surgical emergencies. Diagnosis of acute appendicitis still poses a challenge. The most important thing in management of appendicitis is to diagnose at the initial presentation to avoid/reduce the complications of appendicitis and this will help to minimize the negative

appendicectomy rates. When it is diagnosed early chance of morbidity is less and mortality can be avoided. Present study consists of 55 patients with clinically diagnosed appendicitis who were divided into 3groups depending on the histology and intra-operative findings. Group 1 consists of the undetermined group which included chronic appendicitis, lymphoid hyperplasia. Group 2 consisted of inflamed appendicitis patients who did not have any complications like abscess, perforation. Group 3 had complicated appendicitis. Group2 and group3 were together considered as acute appendicitis proved histologically. All 3 groups were compared with respect to various inflammatory markers like WBC, CRP, IL-6, IL-8 and TNF-α. Vinoth *et al.,* (2011) showed that incidence of appendicitis was more common in male as compared to female. Buckius *et al.,* (2012) and other studies Oguntola *et al.,* (2010) and Ayoade *et al.,* (2006) have also showed higher incidence of appendicitis in male compared to female.

Various studies on CRP showed sensitivity of 40-94% and specificity of 38-87%. Kaya *et al.,* (2012) showed that PPV, NPV of CRP is 0.98 and 0.13. Yildirim *et al.,* (2006) showed that CRP is helpful in perforated appendicitis. Broker *et al.,* (2012) said that perforation of the appendix can be predicted by CRP level. Afsar *et al.,* (2000) showed that the sensitivity and specificity of CRP was 93.6% and 86.6%. Whereas Amalesh *et al.,* (2004) showed that sensitivity, specificity, PPV, NPV were 42%, 91%, 88% and 48% respectively and it may not be an useful tool in diagnosing acute appendicitis.

In our study, 38 patients had WBC count above 11000 which is shown in table 21 and chart 10. Table 26 shows that the mean value of WBC in undetermined was 10469, in inflamed it was 12552 and in complicated appendix it was 14035. This was statistically significant (p value 0.044). Table 27 shows that the mean value of WBC in acute appendicitis was 13152 which in comparison with undetermined group were statistically significant (p value 0.029) As per ROC analysis, Comparison between inflamed (group 2) and undetermined (group 1) showed that WBC count was not significant (p 0.11) whereas when compared between complicated (group 3) and undetermined (group 1) it was very significant (p 0.008). Study on interleukin-6 has showed conflicting results. Turkyilmaz *et al.,* (2006) showed that IL-6 is valuable in diagnosing advanced appendicitis. Yildirim *et al.,* (2006) said that IL-6 might predict perforated appendix and also help in complications. Erkasap *et al.,* (2000) showed that IL-6 may not be very helpful in acute appendicitis. Eriksson *et al.,* (1995) showed that measurement of IL-6 does not increase the accuracy of diagnosing acute appendicitis. Gurleyik *et al.,* (2002) also proved that IL-6 may not be of benefit in increasing the accuracy of the diagnosis of appendicitis. Lapovets (2010) showed that the levels of TNF-α considerably increases in patients with phlegmonous appendicitis. TNF-α is a pro-inflammatory cytokine and has been implicated in pathogenesis of infectious diseases (Wilson *et al.,* 1997). Huang *et al.,* (2012) showed that TNF-α were significantly elevated in acute appendicitis. Turkyilmaz *et al.,* (2006) said that TNF-α was not valuable in acute appendicitis.

Conclusion

Appendicitis has higher incidence among males and complications were also higher in males. Incidence was more common among younger age group. All inflammatory markers were useful in inflamed appendicitis except CRP.

CRP was most useful in predicting complication of acute appendicitis along with IL-8 and TNF-A.WBC and CRP have been traditional investigation in the diagnosis of appendicitis since time immemorial. Novel inflammatory markers like IL-6, IL-8, TNF-A have been introduced off late and have a future application to predict acute inflammation and to decide on surgery prior to complication and also decrease unnecessary appendicectomies but they are expensive for day to day practice though of a good academic value. Clinical examination combined with radiological investigations and inflammatory markers may be more accurate in predicting acute appendicitis. CT and MRI have a definite role to diagnose the complications and to exclude non appendiceal pathology. More studies on the utility of these markers would be useful in management of acute appendicitis.

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