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RESEARCH ARTICLE

HYPERBILIRUBINEMIA AS A NEW DIAGNOSTIC MARKER OF ACUTE APPENDICITIS

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ABSTRACT

Introduction: Appendicectomy is the most frequently performed urgent abdominal operation, often the first major procedure performed by a surgeon in training. Recently, elevation in serum bilirubin was reported in acute appendicitis, but the importance of the elevated total bilirubin has not been stressed. This study aims to evaluate the sensitivity, specificity, positive and negative predictive value of serum bilirubin as a diagnostic marker of acute appendicitis and its complications.

Material and Methods: This prospective study was performed on 100 consecutive patients who were operated on for treatment of acute appendicitis. Clinical diagnosis of acute appendicitis was based on symptoms of abdominal pain, migration of pain, nausea, vomiting, anorexia, fever and signs of peritoneal inflammation like right iliac fossa tenderness, rebound tenderness and guarding. Apart from the routine investigation all the 100 cases were subjected specifically to the following four investigations i.e. Total WBC count, Differential Leukocyte count, CRP and Serum Bilirubin, to evaluate their role in accurately diagnosing a case of acute appendicitis.

Results: Of total 100 patient operated for acute appendicitis or its complications, histopathology shows signs of inflammation in only 80. So out of 80 cases of acute appendicitis, 57 (71.25%) had elevated Serum Bilirubin. In those cases 19 (23.75%) had appendicitis associated with complications and 38 (47.5%) had appendicitis without any complications. In the rest 23 (28.75%) patients Serum Bilirubin were normal.

Conclusion: The sensitivity, Specificity, predictive value of positive test and predictive value of negative test of Serum Bilirubin in my study is 71.25%, 80%, 93% and 41% respectively.. Patients with clinical signs and symptoms of appendicitis and with hyperbilirubinemia higher than the normal range should be identified as having a higher probability of Acute appendicitis associated with complications suggesting, serum bilirubin levels have a predictive potential for the diagnosis of Acute appendicitis associated with complications.

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INTRODUCTION

Acute appendicitis is the commonest cause of "Acute Surgical abdomen (O' Connel, 2008; Smink and Soybel, 2007)". The diagnosis of Appendicitis still remains a dilemma in spite of advances in the radiological and laboratory investigations. The percentage of appendicectomies performed where appendix subsequently found to be normal varies 15- 50% (Deutsch *et al*., 1983) and postoperative complications can occur in up to 50% (Piper *et al*., 1982) of these patients. Delay in diagnosis of Acute Appendicitis leads to perforation and peritonitis and increased mortality.

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To supplement the clinical diagnosis and to reduce the frequency of unnecessary Appendicectomy, the importance of laboratory investigations like White Blood Cell (WBC) counts and C-reactive protein (CRP) etc values has been stressed (Grönroos, 1999). The use of Ultrasonography (USG) as a diagnostic tool for appendicitis has been widely known and studied. Various scores combining clinical features and laboratory investigations have also been developed and are good enough to reach the diagnosis. These are the Alvarado score (Alvarado, 1986) and the Modified Alvarado score (Kalan *et al*., 1994). Importance of hyperbilirubinemia or elevated Serum Bilirubin and its association in acute appendicitis has being postulated recently. It is hypothesized that an association exists between hyperbilirubinemia and acute appendicitis and its complications such as appendicular

perforation (Estrada *et al*., 2007). This study aims to evaluate serum bilirubin as a marker of acute appendicitis and its complications, in alone or combination with other marker like CRP, total leukocyte count, and neutrophil count to improve diagnosis of appendicitis and decision making, hence decreases negative and unnecessary appendicectomies.

MATERIALS AND METHODOS

This prospective study was performed on 100 consecutive patients who were operated on for treatment of acute appendicitis. For establishing the diagnosis careful patient history was obtained at first. Physical examination of the patient by a surgeon, followed by some routine laboratory tests and radiographs.

Inclusion criteria

All patients above the age of 10 years diagnosed clinically to have Acute Appendicitis and subjected for Appendicectomy at Department of General Surgery, Rajendra Institute of Medical Sciences, Ranchi.

Exclusion criteria

- Patients with co-morbid conditions were not included in the study.
- Patients who were managed conservatively were also excluded from the study.
- Patients admitted for interval appendicectomy following recurrent appendicitis or appendicular mass previously treated conservatively, were also excluded.
- Concomitant conditions where CRP/Leukocyte count/Neutrophil count is elevated in acute appendicitis patients with associated diseases like:
- Rheumatoid arthritis
- SLE
- Glomerular nephritis
- Gout
- Inflammatory bowel disease
- Any other conditions where CRP was raised
- All patients documented to have a past history of:
- Jaundice or Liver disease.
- Chronic alcoholism (that is intake of alcohol of > 40 g/day for Men and > 20 g/day in Women for 10 years).
- Hemolytic disease.
- Acquired or congenital biliary disease.
- All patients with positive HBsAg.
- All patients with cholelithiasis.
- All patients with cancer of hepato-biliary system.

RESULTS

Statistical Analysis: The data was analyzed by using SPSS 20 software. The data is presented in percentages, rates and ratios. Chi square test was used to find the association between attributes. Of total 80 cases of acute appendicitis 57 (71.25%) had elevated Serum Bilirubin. In the rest, rest 23 (28.75%) patients Serum Bilirubin were normal [Table-1].

Table 1. Correlation of Serum Bilirubin with Histopathologically positive and negative cases

Elevated Serum Bilirubin	HPE		Total
	Positive	Negative	
Positive	57	04	61
Negative	23	16	39
Total	80	20	100

χ^2 – 17.665; DF = 1; p value = 2.6 (not significant) p<0.05.

Sensitivity	71.25%
Specificity	80%
Predictive value of positive test	93%
Predictive value of negative test	41%

In the present study, all 80 patients had either/or all of the four investigations elevated, i.e. none of them had all four investigations normal (100% true positive). None of the patients, who had all four investigations as normal, had acute appendicitis (0% false negative). Four patients had false positive and 16 patients had true negative [Table-2].

Table 2. Correlation of combining C - reactive protein, WBC count, neutrophil count and Serum Bilirubin with histopathologically positive

CRP, WBC Count Neutrophil Count & Serum Bilirubin	HPE		Total
	Positive	Negative	
Positive	80	04	61
Negative	00	16	39
Total	80	20	100

χ^2 – 76.1905; DF = 1; p value = 0 (significant) p<0.05.

Sensitivity	100%
Specificity	80%
Predictive value of positive test	95.25%
Predictive value of negative test	100%

Out of 80 cases of acute appendicitis 57 (71.25%) had elevated Serum Bilirubin. In those cases 19 (23.75%) had appendicitis associated with complications and 38 (47.5%) had appendicitis without any complications [Table -3].

Table 3. Evaluation of the role of Serum Bilirubin in diagnosis of acute appendicitis associated with complication by correlation with HPE reports

Serum Bilirubin	HPE		Total
	Acute Appendicitis with complication	Acute Appendicitis without complication	
Positive	19	38	57
Negative	06	17	23
Total	25	55	80

χ^2 – 0.4005; DF = 1; p value = 0.526817 (not significant) p<0.05.

Sensitivity	76%
Specificity	31%
Predictive value of positive test	33.3%
Predictive value of negative test	74%

Bilirubin levels (mg/dL)	HPE			
	Acute appendicitis without complication		Acute appendicitis with complication	
	Mean	SD	Mean	SD
Total Bilirubin	1.4	0.65	1.9	1.16

DISCUSSION

Clinical diagnosis was found to be correct in 80% of cases and hence the rate of negative laparotomies for acute appendicitis in our study is 20%. According to literature, accuracy of clinical examination ranges from 75 to 97%, depending on experience of surgeon the reported rate of negative appendicectomy is 20-30%. These results when compared with other studies are as follows. Amongst the patients diagnosed with Acute appendicitis without perforation (n=81), 58 patients (71.6%) were found to have elevated bilirubin (>1.0 mg/dL) while only 23 patients (28.4%) had normal bilirubin levels (≤1.0 mg/dL).

	Study Group	HPE Positive	HPE Negative	Negative Appendicectomy (%)
Gurleyik *et al*	108	90 (83.3%)	18 (16.6%)	16.6%
Shakhatreh HS *et al*	98	89 (91%)	9 (9%)	9%
Asfar *et al*	78	63 (80%)	15 (20%)	20%
Oosterhuis *et al*	125	101 (80.8%)	24 (19.2%)	19.2%
Khan *et al*	259	222 (85.7%)	37 (14.3%)	14.3%
Present study	100	80	20	20%

In patients diagnosed with Appendicular perforation (n=19), 16 patients (84.21%) had bilirubin elevated (>1.0 mg/dL), while only 3 patients (15.79%) had normal levels (>1.0 mg/dL). Thus, Hyperbilirubinemia was found in most of the patients diagnosed with acute appendicitis (71.6%) or Appendicular perforation (84.21%). Estrada *et al*. (2007) had found hyperbilirubinemia in 59 (38%) of 157 patients studied with acute appendicitis. Sand *et al*. (2009) in his study found the mean bilirubin levels in patients with Appendicular perforation to be significantly higher than those with a non-perforated appendicitis.

The role of combining WBC count, CRP Count, Neutrophil Count and Serum Bilirubin in diagnosis of Acute Appendicitis. Marchand *et al*. (1983) in their study suggested that combination of these tests has 100 % sensitivity and 50 % specificity in the diagnosis of acute appendicitis. Gronroos and Gronroos *et al*. (1999) concluded that acute appendicitis is very unlikely when all the tests are normal, and acute appendicitis can be excluded with a 100 % predictive value. NG Kim-Choy, Lai Shih-Wei (2002) found that if the combination of elevated C reactive protein, leucocytosis and elevated neutrophil count was used, satisfactory specificity and positive predictive value were achieved in diagnosing acute appendicitis. M N Khan (2004) in their study stated that, both the inflammatory markers i.e. WBC and CRP can be helpful in the diagnosis, when measured together it increases their positive predictive value.Yang *et al*. (2005) in their study concluded that patients with normal results in all these tests were highly unlikely to have acute appendicitis and should be evaluated with extra caution before surgery.

In the present study, it was observed that none of the cases of acute appendicitis had all the four tests within normal limits. The predictive value of negative test in the present study is 100 % i.e. if all four tests are negative acute appendicitis can be excluded. In our study, four patients the tests were false positive and it was observed that two of them had other intra-abdominal causes of elevation of CRP and WBC count .Also combining the tests increases the sensitivity, specificity and predictive value of positive tests. The significance of association of combining the tests and their role in diagnosing acute appendicitis is found to be very high. Amongst the patients diagnosed with Acute appendicitis (80), 57 patients (71.25%) were found to have elevated bilirubin (>1.0 mg/dL) while only 23 patients (28.75%) had normal bilirubin levels (≤1.0 mg/dL). In patients diagnosed with Acute appendicitis with associated complications (25), 19 patients (76%) had bilirubin elevated (>1.0 mg/dL), while only 6 patients (24%) had normal levels (≤1.0 mg/dL). Thus, Hyperbilirubinemia was found in most of the patients diagnosed with Acute appendicitis with associated complications. Sand *et al*. (2009) in his study found the mean bilirubin levels in patients with Appendicular perforation to be significantly higher than those with a non-perforated appendicitis. The sensitivity in our study was more than that by Sand *et al*. (2009) in which, he found the sensitivity and specificity in his study of hyperbilirubinemia for predicting Appendicular perforation to be 70% and 86.0% respectively.

Conclusion

Serum bilirubin levels appears to be a promising new laboratory marker for diagnosing acute appendicitis, however diagnosis of appendicitis remains essentially still - clinical. Its level come out to be a credible *aid* in diagnosis and would be helpful investigation in clinical decision making for appendectomy.

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