ORIGINAL RESEARCH

Evaluation of hyperbilirubinemia as a diagnostic marker for acute appendicitis and its role in the prediction of appendicular perforation

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Abstract

Introduction: Acute appendicitis is one of the commonest causes of “Acute Surgical Abdomen”. Even though the field of medicine has witnessed significant advancement in radiological and laboratory investigations, none the less the diagnosis of Appendicitis remains a dilemma. Experienced clinicians can accurately diagnose appendicitis based on a combination of history, physical examination and laboratory studies in about 80% of the cases. Delay in the diagnosis of Acute Appendicitis is likely to lead to perforation and peritonitis and hence increased mortality and morbidity making it a double-edged sword. Surgical delay in prompt management of the subjects with appendicitis leads to dreadful complications like gangrenous changes and perforation of the appendix. Recently, rise in level serum bilirubin has been reported in acute appendicitis and appendicular perforation, but the importance of the raised total bilirubin has not been stressed. The present study was undertaken to assess the relationship between hyperbilirubinemia and acute appendicitis or appendicular perforation.

Material and methods: A total of 50 consecutive cases diagnosed as acute appendicitis and appendicular perforation, based on clinical examination and various investigations, and subjected to Open or Laparoscopic Appendicectomy, were studied. Pre-operatively, patient’s blood was taken for estimating serum bilirubin, serum liver enzyme levels, total white blood cell count and differential leukocyte count. Diagnosis of acute appendicitis or appendicular perforation was correlated with levels of serum bilirubin.

Results: Level of Serum Bilirubin was raised in cases of acute appendicitis but much more in appendicular perforation as compared to uncomplicated acute appendicitis.

Conclusion: Serum bilirubin levels appear to be a promising laboratory marker for diagnosing acute appendicitis. Bilirubin levels come out to be a credible aid in diagnosis of acute appendicitis and would be a helpful investigation in decision making.

Keywords: Acute Appendicitis, Appendicular Perforation, Serum Bilirubin.

Introduction

For decades, the appendix was erroneously considered as a vestigial organ with no known function. It is now well established that the appendix is an immunologic organ that actively
secretes immunoglobulins, particularly immunoglobulin A (IgA).\(^{(1)}\) The vermiform appendix is important in surgical practice primarily due to its susceptibility to inflammation resulting in acute appendicitis. The overall lifetime risk of developing appendicitis is approximately 7% (8.6% for males and 6.7% for females).\(^{(2)}\) The male: female ratio is 1.4:1 (range is M:F = 1:1 to 3:1).\(^{(2)}\) The incidence of acute appendicitis is decreasing steadily since late 1940 with the present incidence rate of approximately up to 110 (starting from 55.3 in females and 68.8 in males) cases per 10,000 population per year.\(^{(3)}\) Acute appendicitis is one of the commonest causes of “Acute Surgical Abdomen”. Appendicectomy is the most frequently performed emergency abdominal operation and is often the first major procedure performed by a surgeon in training.\(^{(4)}\) Even though the field of medicine has witnessed significant advancement in radiological and laboratory investigations, not the less the diagnosis of Appendicitis remains a dilemma. Experienced clinicians can accurately diagnose appendicitis based on a combination of history, physical examination and laboratory studies in about 80% of the cases.\(^{(5)}\) Mostly, Acute Appendicitis can be easily diagnosed, however, in some cases, the symptoms and signs are variable, and a firm diagnosis is difficult to make. This is particularly true where the appendix is retrocaecal or retroileal. The percentage of negative appendicectomies performed where the appendix was subsequently found to be normal varies between 15-50%.\(^{(6)}\) Delay in the diagnosis of Acute Appendicitis is likely to lead to perforation and peritonitis and hence increased mortality and morbidity making it a double-edged sword.\(^{(7,8)}\) Most subjects with acute appendicitis present with the cardinal symptoms and signs of low-grade pyrexia, localized abdominal tenderness, muscle guarding, rebound tenderness, and limitation of respiratory movement in the lower abdomen on inspection. But in atypical presentations, diagnostic confusion and delay in treatment may occur. Crohn's disease, ectopic pregnancy, diverticulitis, endometriosis, mittelschmerz, mesenteric adenitis, omental torsion, pelvic inflammatory diseases, ruptured ovarian cyst, urinary tract infection may all mimic acute appendicitis. The Worldwide mean value for difference in diagnostic error rate ranges from 12 to 23% and 24–42% respectively in men and women.\(^{(9)}\) Surgical delay in prompt management of the subjects with appendicitis (not with perforation, in particular), either due to delay in presentation (particularly in males with retrocaecal or retroileal position) or misjudgment, leads to dreadful complications like gangrenous changes and perforation of the appendix. Gangrene or perforation further leads to more complications like appendicular abscess formations, localized/generalized peritonitis, faecal fistula formation, intestinal obstruction due to adhesion formation, portal pyemia, sepsis, and sterility in women of childbearing age (though recent studies deny it as a major risk factor) with overall increased morbidity and prolonged hospital stay.\(^{(2,10)}\) In adults, the incidence of appendicular perforation is 13–37%.\(^{(11)}\) The mortality rate for uncomplicated is 0.1–0.5%, while that of perforated appendicitis is much higher, ranging from 3% overall to as high as 15% in elderly subjects.\(^{(12)}\) On the contrary, in case of diagnostic difficulties and atypical presentations, if appendicectomy is performed based on clinical suspicion only, may increase the number of unnecessary appendicectomies (up to20%).\(^{(13)}\) Recently, rise in level serum bilirubin has been reported in acute appendicitis and appendicular perforation, but the importance of the raised total bilirubin has not been stressed. It is well established that when microbes invade the body, leukocytes defend it resulting in elevated leukocyte count. Bacterial invasion in the appendix leads to the transmigration of bacteria and the release of pro-inflammatory cytokines such as TNF-alpha, IL6, and cytokines. These reach the liver via the Superior mesenteric vein (SMV) and may produce inflammation, abscess, or dysfunction of the liver either directly or indirectly by altering the hepatic blood flow. Nearly 80% of blood supply to the liver comes from the portal venous system, which carries absorbed substances including bacteria and toxins from
the intestine. Normally, a small number of bacteria and their toxic products get cleared after entering the liver by detoxification and immunological action of the reticuloendothelial system. But kupffer cells may fail to clear the overabundant bacterial load incase of complicated acute appendicitis which in turn damage hepatocytes and raise serum bilirubin level. Bacteraemia leads to endotoxemia with resultant impaired excretion of bilirubin from the bile canaliculi. Interleukin-6 (IL6) and tumor necrosis factors (TNF) are also considered to depress excretory functions of the liver resulting in hyperbilirubinemia without a rise in liver enzymes level (14-20).

The present study was undertaken to assess the relationship between hyperbilirubinemia and acute appendicitis and to evaluate its credibility as a diagnostic marker for acute appendicitis and also, to see whether raised bilirubin levels have a predictive potential for the diagnosis of appendicular perforation.

**Material and methods**

This prospective study was conducted on 50 patients admitted to Surgical Emergency with acute abdomen, proven to be a case of Appendicitis/ Appendicular perforation on the basis of clinical examination and investigations (X-ray Abdomen, USG Whole Abdomen and CECT Abdomen if needed) were selected randomly for this study. These patients were evaluated on the basis of signs and symptoms and investigations.

**Inclusion Criteria**

- All patients diagnosed as acute appendicitis and confirmed on histopathological report.
- All patients diagnosed as appendicular perforation and confirmed on histopathological report.

**Exclusion Criteria**

- All patients documented to have a past history of:
  - Jaundice or Liver disease.
  - Chronic alcoholism (that is intake of alcohol more than 40 g/day for men and more than 20 g/day in Women for 10 years).
  - Hemolytic disease.
  - Acquired or congenital biliary disease.
  - All patients with positive HBsAg/HCV/HIV.
  - All patients with cholelithiasis.
  - All patients with cancer of hepato- biliary system.

Pre-operatively, patient’s blood was taken for estimating serum bilirubin, serum liver enzyme levels, total white blood cell count and differential leukocyte count.

**Statistical analysis**

- Mean of the level of elevation of Serum bilirubin was calculated for patients with final diagnosis of Acute Appendicitis and Appendicular Perforation.
- Also, Sensitivity, Specificity, Positive predictive value, Negative predictive value and Odds ratio were determined by 2 x 2 tables.

**Results**

The age group 11-20 years was affected the most (44%) followed by age group 21-30 (34%). The youngest patient in this study was a 2 year old female while the oldest patient was a 68 year old male (Table 1). Of 50 patients enrolled for the study, 27 patients (54%) were male while the remaining 23 patients (46%) were female. The
rise in serum bilirubin levels above the normal value was seen in more than 2/3rd of patients of acute appendicitis, hence signifying the occurrence of hyperbilirubinemia in appendicitis (Table 1). Out of 40 patients diagnosed as uncomplicated acute appendicitis, 25 patients had raised bilirubin levels while the remaining 15 patients had normal levels. Thus, hyperbilirubinemia was found in most of the patients (62.5%) diagnosed as acute appendicitis (Table 2). Out of 10 patients diagnosed as Appendicular perforation, 9 patients had raised bilirubin levels, while the remaining 01 patient had normal levels. So it was seen that hyperbilirubinemia was present in more fraction of patients (90%) of appendicular perforation as compared to the patients of acute appendicitis (62.5%) (Table 3). 25 patients (62.5%) of the total patients diagnosed with Acute appendicitis (n=40) were found to have elevated bilirubin levels (> 1.0 mg/dL) while 15 patients (37.5%) had normal bilirubin levels (≤ 1.0 mg/dL). Similarly, 9 patients (90%) of the total patients diagnosed with Appendicular perforation (n=10) were found to have elevated bilirubin levels (> 1.0 mg/dL) while 01 patient (10%) had normal bilirubin levels (≤1.0 mg/dL) (Table 4).

Table 1: Total bilirubin levels

<table>
<thead>
<tr>
<th>Total bilirubin (mg/dL)</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1.0</td>
<td>16</td>
<td>32.0</td>
</tr>
<tr>
<td>&gt; 1.0</td>
<td>34</td>
<td>68.0</td>
</tr>
<tr>
<td>Total</td>
<td>50</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Table 2: Bilirubin levels in uncomplicated acute appendicitis

<table>
<thead>
<tr>
<th>Total bilirubin (mg/dL)</th>
<th>Distribution in Patients with uncomplicated Acute Appendicitis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
</tr>
<tr>
<td>&gt; 1.0</td>
<td>25</td>
</tr>
<tr>
<td>≤ 1.0</td>
<td>15</td>
</tr>
<tr>
<td>Total</td>
<td>40</td>
</tr>
</tbody>
</table>

Table 3: Bilirubin levels in patients with Appendicular perforation diagnosis

<table>
<thead>
<tr>
<th>Total bilirubin (mg/dL)</th>
<th>Distribution in Patients with Appendicular perforation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
</tr>
<tr>
<td>&gt; 1.0</td>
<td>09</td>
</tr>
<tr>
<td>≤ 1.0</td>
<td>01</td>
</tr>
<tr>
<td>Total</td>
<td>10</td>
</tr>
</tbody>
</table>

Table 4: Correlation of Acute Appendicitis and Appendicular Perforation with total serum bilirubin levels.

<table>
<thead>
<tr>
<th>Serum bilirubin (mg/dL)</th>
<th>Final diagnosis (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Acute appendicitis (n=40)</td>
</tr>
<tr>
<td></td>
<td>Number</td>
</tr>
<tr>
<td>&gt;1.0</td>
<td>25</td>
</tr>
<tr>
<td>≤ 1.0</td>
<td>15</td>
</tr>
<tr>
<td>Total</td>
<td>40</td>
</tr>
</tbody>
</table>

Discussion

In the present study on the 50 patients, 27 patients (54%) were males while the remaining 23 patients (46%) were females. The mean age in our study population (50 patients) was 22.36 ± 11.15 years (range 02 to 68 years). This is consistent with the quoted incidence of
Appendicitis in the literature where it is most frequently seen in patients in their second through fourth decades of life. Hyperbilirubinemia (> 1.0 mg/dL) was found in 34 patients (68%) of all the 50 patients, while 16 patients (32%) had normal bilirubin levels (≤1.0 mg/dL). Estrada et al (12) had found hyperbilirubinemia in 59 (38%) of 157 patients studied with acute appendicitis. Amongst the patients diagnosed with Acute appendicitis without perforation (n=40), 25 patients (62.5%) were found to have elevated bilirubin (>1.0 mg/dL) while only 15 patients (37.5%) had normal bilirubin levels (≤1.0 mg/dL). In patients diagnosed with Appendicular perforation (n=10), 9 patients (90%) had bilirubin elevated (>1.0 mg/dL), while only 1 patient (10%) had normal levels (≤1.0 mg/dL). Thus, Hyperbilirubinemia was found in most of the patients diagnosed with acute appendicitis (62.5%) or Appendicular perforation (90%). Atahan K et al (23) found hyperbilirubinemia in 16.3% of patients diagnosed as acute appendicitis and 80% of patients diagnosed with appendicular perforation. The mean bilirubin levels in patients diagnosed with Acute appendicitis was 1.18 ±0.37 mg/dL (range 0.6– 2.20 mg/dL) while in patients diagnosed with Appendicular perforation was 2.3±0.85 mg/dL (range 1.0 –3.40 mg/dL). Hence, It was concluded that patients with Appendicular perforation had higher levels of bilirubin as compared to that of acute appendicitis. So it was observed that the patients with features suggestive of appendicitis with higher values of bilirubin, are more likely to have Appendicular perforation than those with normal or slightly elevated total serum bilirubin. Sand et al (24) 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, Specificity, was calculated from a 2x2 table. In our study, Sensitivity and Specificity of bilirubin in predicting acute appendicitis and Appendicular perforation as diagnosis was 90% and 62.5% respectively. The sensitivity in our study was more than that by Sand et al (24) in which, he found the sensitivity and specificity in his study of hyperbilirubinemia for predicting Appendicular perforation to be 70% and 86.0% respectively. In our study, odds ratio was found to be 5.4. Estrada et al (12) described the odds of appendiceal perforation to be 3 times higher for patients with hyperbilirubinemia compared with those with normal bilirubin levels.

Summary and conclusion
Acute appendicitis is the most common cause of “acute abdomen” in young adults. Diagnosis of Appendicitis still remains a dilemma in spite of the advances in various laboratory and radiological investigations. Serum bilirubin levels appear to be a promising new laboratory marker for diagnosing acute appendicitis, however the diagnosis of appendicitis is essentially still clinical.

The significant findings in our study are
• The Sensitivity and Specificity of serum bilirubin as a marker in predicting Appendicular perforation was 90% and 62.5% respectively.
• The Positive predictive value and Negative predictive value for the same was 26.4% and 93.75% respectively.
• The Odds ratio was calculated to be 5.4.

The present study suggests
• Serum bilirubin levels appears to be a promising new laboratory marker for diagnosing acute appendicitis, however diagnosis of appendicitis still remains essentially clinical. Bilirubin levels come out to be a credible aid in diagnosis of acute appendicitis and would be a helpful investigation in decision making.
• 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 Appendicular perforation suggesting, serum bilirubin levels have a predictive potential for the diagnosis of Appendicular perforation.
Bibliography
22. Flum DR, Morris A, Koepsell T, Dellinger EP. Has misdiagnosis of appendicitis
