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# A CORRELATIVE STUDY OF HYPERBILIRUBINEMIA AND ELEVATED LIVER ENZYMES IN GANGRENOUS OR PERFORATED APPENDICITIS

Surgery

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## ABSTRACT

**Purpose:** Aim is to study the relationship between hyperbilirubinemia and elevated liver enzymes and acute appendicitis and to evaluate its credibility as a diagnostic marker for acute appendicitis.

**Materials and methods:** This is a prospective study conducted at the Chengalpattu Medical College Hospital, Chengalpattu, Tamilnadu, India between september 2017 to january 2018 were studied on 100 consecutive cases of acute appendicitis admitted to the emergency ward. These cases were also subjected to liver function tests and clinical diagnosis was confirmed perioperatively and post-operatively by histopathological examination.

**Results:** As in perforated acute appendicitis there is altered liver function like evidenced by elevated liver enzymes and hyperbillirubinemia.

**Conclusion:** Finding of the present study suggest Serum bilirubin levels and liver enzyme appears to be a promising new laboratory marker for diagnosing acute appendicitis with perforation.

## KEYWORDS

Appendiceal Perforation,LFT,Hyperbillirubinemia,Liver Enzymes

### OBJECTIVES

1) To study the relationship between hyperbilirubinemia and elevated liver enzymes and acute appendicitis and to evaluate its credibility as a diagnostic marker for acute appendicitis.
2) To evaluate whether elevated bilirubin and liver enzymes levels have a predictive potential for the diagnosis of appendicular perforation.

### INTRODUCTION

Pathophysiology behind the elevation of serum bilirubin in acute appendicitis.Both increased bilirubin production and alteration in bilirubin clearance can lead to bilirubin accumulation and may be involved in the hyperbilirubinemia observed in patients with appendix perforation[1]. It has frequently been demonstrated that several bacterial infections accompanying hepatic dysfunction, to the extent that anomalies in bile flow and bile acid production arise as a result

These patients together with those who have extra hepatic bacterial infections demonstrated cholestasis induced by nitric oxide and a pro inflammatory cytokines[2,3]. In addition, the most common bacterial species cultured from the appendix walls of patients with acute appendicitis are Escherichia coli and bacteroides fragilis (80%), two species that inhibit microcirculation and cause sinusoidal damage as shown in rat liver model.

Lipo-polysaccharides associated with Escherichia coli can affect hepatocyte uptake and bile acid secretion and further research involving a rat liver model has shown that eschericha coli cause a dose dependent cholestasis disorder. In addition, Escherichia coli infection leads to regular hemolysis of erythrocytes, increased bilirubin load and, perhaps the development of hyperbilirubinemia may be a consequence of this mechanism[4,5,6]

### METHODOLOGY

### SOURCE OF DATA

- All patients admitted with clinical diagnosis of acute appendicitis or appendicular perforation under general surgery in Chengalpet medical college and hospital, chengalpet taken as subjects for this study
- After taking the proposed informed consent data were collected using the questionnaire/ proforma.
- The primary data for this study were the blood investigations of the patients.

### METHOD OF COLLECTION OF DATA

The following tests were carried out for patients diagnosed as acute appendicitis or gangrenous or appendicular perforation under general surgery and admitted to chengalpet medical college and hospital ,

1. Complete blood count
2. Serum bilirubin (total and direct bilirubin)
3. C-reactive protein
4. Liver enzymes (SGP ,SGOT , ALP )
5. Seropositivity for HbsAg and HCV
6. Ultrasonography of abdomen and pelvis

### INCLUSION CRITERIA

- Patients of 18 years of age and above scheduled for appendectomy for acute appendicitis at emergency unit of our hospital.
- All patients diagnosed as gangrenous or appendicular perforation clinically on admission, for both these groups, only patients with histopathological report suggestive of appendicitis would be included.

### EXCLUSION CRITERIA

- Age below 18 years
- Patient with appendicular ;ump
- Previous history of chronic alcoholic liver disease
- Hemolytic or liver disease associated with hyperbilirubinemia
- Previous history of any malignancy
- History of drug induced hepatitis
- All patients with positive HbsAg
- Patients on hepatotoxic drugs

### RESEARCH HYPOTHESIS

Hyperbilirubinemia as a new biochemical marker in acute appendicitis and also it has role in predicting appendicular perforation.

### PROCEDURE

This is a prospective study conducted at the Chengalpet Medical College Hospital, Chengalpet, Tamilnadu, India between september 2017 to january 2018 were studied on 100 consecutive cases of acute appendicitis admitted to the emergency ward. These were subjected to investigations to support the diagnosis. These cases were also subjected to liver function tests and clinical diagnosis was confirmed perioperatively and post-operatively by histopathological examination. Their clinical and investigative data were compiled and analyzed. Statistical analysis was performed.

Ethical clearance for the study was obtained from institutional ethics committee CHENGALPET MEDICAL COLLEGE AND HOSPITAL , CHENGALPET. Based on the selection criteria patients admitted with clinical diagnosis of acute appendicitis or gangrenous or

appendiceal perforation under department of general surgery, CHENGALPET MEDICAL COLLEGE AND HOSPITAL during the study period were screened for eligibility. The eligible patients were briefed about the nature of the study and a written informed consent was obtained from the consented patients. Thorough history was taken and clinical examination was done for all patients and findings were recorded on predesigned and pretested Proforma.

These investigations are required as routine before taking any patient for appendicectomy:

1. Complete blood count
2. Urine routine
3. Serum bilirubin (total & direct bilirubin )
4. C-reactive protein
5. Liver enzymes ( SGPT, SGOT , ALP )
6. Seropositivity for HbsAg and HCV
7. Ultrasonography of abdomen and pelvis
8. Serum creatinine.

In our study serum total bilirubin more than 1.2mg/dl is considered as hyperbilirubinemia.

The serum bilirubin and LFTs were carried out by using the auto analyser machine ERBA chem.-5 Plus available in our hospital and HbsAg was tested by ELISA using HEPACARD kit.

## RESULTS

A total of 100 patients with clinical diagnosis of acute appendicitis or appendiceal perforation were enrolled in the study and studied.

Of the 100 patients enrolled for the study, 70 patients (70 %) were males while the remaning 30 patients (30%) were females

The mean age in our study population (100 patients) was 29.16 +/- 11.21 years. The average age group in males 29.24 +/- 11.64 years was slightly higher than females 28.96 +/- 10.33 years

**LIVER FUNCTION TESTS**

| PARAMETERS | MEAN | SD |
|---|---|---|
| Total bilirubin | 1.7 | 1.0 |
| Conjugate | 0.57 | 0.42 |
| Unconjugate | 1.13 | 0.83 |
| SGOT | 26.38 | 6.59 |
| SGPT | 21.12 | 6.09 |
| ALP | 37.52 | 14.34 |

**TOTAL BILIRUBIN LEVELS IN ALL PATIENTS (N=100)**

| Total bilirubin | Number | percentage | Intra operative or HPE | |
|---|---|---|---|---|
| | | | AA | AP |
| <1.2 | 53 | 53% | 51 | 2 |
| >1.2 | 47 | 47% | 19 | 28 |
| Total | 100 | 100% | 70 | 30 |

**Bilirubin levels in patients with acute appendicitis diagnosis ( intraoperative / HPE )**

| Total Bilirubin | Number | Percentage |
|---|---|---|
| <1.2 | 51 | 72.86% |
| >1.2 | 19 | 27.14% |
| Total | 70 | 100% |

**Bilirubin levels in patients with appendicular perforation diagnosis (intra operative/ HPE )**

| Total Bilirubin | Number | Percentage |
|---|---|---|
| <1.2 | 2 | 6.66% |
| >1.2 | 28 | 93.34% |
| Total | 30 | 100% |

**Comparison of mean serum bilirubin levels in patients with acute appendicitis and appendicular perforation (intraoperative)**

| Bilirubin levels | Acute appendicitis (N=70) | | Appendiceal perforation (N=30) | | P-value | Conclusion |
|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | | |
| Total Bilirubin | 1.23 | 0.81 | 2.9 | 0.75 | <0.0001 | Significant |
| Conjugate | 0.44 | 0.34 | 0.86 | 0.44 | <0.0001 | Significant |
| Unconjugate | 0.74 | 0.54 | 2.04 | 0.68 | <0.0001 | Significant |

## DISSCUSION

In this study of 100 patients, hyperbilirubinemia was found in patients with gangrenous/perforated appendicitis. This hyperbilirubinemia was mixed in type (both conjugated and unconjugated) in most of the patients and at the same time there was also elevation or minimal elevation (<100 U/L) in ALT and AST in most of the cases[7,8,9,10]. Similarly, ALP was either within the normal range or was minimal to moderately elevated.

Broadly, we can say there is both elevated liver enzymes and hyperbilirubinemia in the majority of cases. Since these findings were documented at the time of admission, it is unlikely that liver injury because of anesthetic agents, blood transfusion, or medication was the cause of elevated bilirubin levels. Moreover, as per our exclusion criteria patients with alcoholic liver disease, viral hepatitis, hemolytic or congenital liver diseases were excluded from the study[11,12,13].

The most likely explanation of the rise in Serum Billirubin and liver enzymes are due to circulating endotoxinemia as a result of appendiceal infection.[14,15] Utili *et al* has shown with *in vitro* infusion of endotoxin into the isolated rat liver that there is a dose-dependent decrease in bile salt excretion from the liver and that it is possible that *Escherichia coli* endotoxin exerts direct damage at the cholangiolar level[16,17].

In Sisson *et al* in 1971demonstrated that in appendicitis mucosal ulceration occurs early and this facilitates invasion of bacteria into the muscularis propria of the appendix thereby causing classical acute suppurative appendicitis. Subsequent events lead to edema, elevated intraluminal pressure, and ischemic necrosis of mucosa, causing tissue gangrene and perforation of the appendix. This process is associated with progressive bacterial invasion most likely facilitated by bacterial cytotoxins.[18,19,20] The number of organisms isolated from patients with gangrenous appendicitis is 5 times greater than those with acute suppurative appendicitis. In Estrada *et al* also found significantly higher peritoneal culture in patients with gangrenous/perforated appendicitis.

This elevated load of bacteria in appendicitis causes either direct invasion or translocation into the portal venous system.[21,22] Direct invasion of bacteria into the hepatic parenchyma interferes with the excretion of bilirubin into the bile canaliculi by a mechanism that is thought to be caused by the bacterial endotoxin and is biochemical in nature rather than obstructive[23,24].

Indirect evidence of bacterial translocation from inflamed gastrointestinal tract or peritonitis to the liver via the portal vein and the development of hepatitis and pyogenic liver abscess was observed by Dieulafoy in his study[25,26,27]. These bacteria commonly reach liver from intra-abdominal organs, commonly from the appendix.

More direct evidence of bacterial translocation from inflamed bowels was observed in clinical and experimental studies. Recently, in one study, blood samples from the superior mesenteric vein in acute appendicitis showed bacteria in 38% of patients.[28] These findings suggest that bacteria may transmigrate and produce portal bacteremia, hepatocellular dysfunction or pyogenic liver abscess. This low percentage of positive blood cultures cannot explain hepatocellular dysfunction in the majority of cases. Thus, there must be other substances involved. It has been shown that liver dysfunction is caused by cytokines released from the gut due to injury/inflammation. Studies proven, rats were subjected to intra-abdominal sepsis from cecal ligation and puncture and the following observations were made: 1) the small intestine is an important source of adrenomedullin release during poly microbial sepsis; 2) nor-epinephrine induced hepatocellular dysfunction in early sepsis, mediated by activation of a-2 adreno-receptors; and 3) TNF produces hepatocellular dysfunction despite normal cardiac output and hepatic microcirculation.[28,29]

And so it is concluded that hepatocellular function is depressed during the early stage of sepsis despite the increased cardiac output and hepatic blood flow and decreased peripheral resistance. The depression of hepatocellular function in the early, hyper-dynamic stage of sepsis does not appear to be due to reduction in hepatic perfusion but is associated with elevated levels of circulating pro-

inflammatory cytokines such as TNF and IL-6. Thus up regulation of TNF and/or IL-6 may be responsible for producing hepatocellular dysfunction during the early hyper-dynamic stage of sepsis.

Our study shows that hyperbilirubinemia with elevation in the liver enzymes is a significant predictor of appendiceal perforation. This was demonstrated by a study by Estrada *et al* and other studies showing nearly a threefold risk of perforated appendicitis in patients with total bilirubin levels greater than 1.2 mg/dL,[30]

Therefore, Serum Billirubin and liver enzymes estimation, a simple cheap and easily available test in every laboratory, can be added to the routine investigation list of clinically suspected case of acute appendicitis for the confirmation of diagnosis.[32,33] Since the rise in Serum Billirubin and liver enzymes level was significantly higher in patients with appendiceal perforation, it has a definite predictive potential in these cases. Therefore, obtaining Serum Billirubin and liver enzymes values upon admission can be used in conjunction with more modern diagnostic tests such as CT scan, ultrasonography of abdomen to help determine the presence of perforation and thus aid in prompt clinical management.

## CONCLUSION

Finding of the present study suggest serum bilirubin levels and liver enzyme appears to be a promising new laboratory marker for diagnosing acute appendicitis with perforation, however diagnosis of appendicitis remains essentially still – clinical. Its levels come out to be a credible aid in diagnosis of acute appendicitis and would be helpful investigation in decision making.

Patients with clinical signs and symptoms of appendicitis and with hyperbilirubinemia three times the normal range and with elevated liver enzymes should be identified as having a higher probability of appendiceal perforation suggesting, serum bilirubin and liver enzymes levels have a predictive potential for the diagnosis of appendiceal perforation.

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