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ORIGINAL ARTICLE

Hyperbilirubinemia has Predictive Potential for the Diagnosis of Appendiceal Perforation

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ABSTRACT

Background: Acute appendicitis is an inflammation of the vermiform appendix. Usually, the diagnosis is made on clinical evaluation and elevated leukocyte count (TLC). But in cases when the clinical diagnosis is indeterminate, additional assessment needs imaging. Despite the increased use of modern diagnostic modalities such as Sonography, computed tomography (CT), and diagnostic laparoscopy, the frequency of misdiagnosis of appendicitis has remained constant (15%) as has the rate of appendiceal rupture. Presently, some serum markers such as C-reactive protein (CRP), lactate, and bilirubin have been proposed as a diagnostic tools for appendicitis. When compared CRP, TLC and lactate are found less explicit than bilirubin as predictive markers for acute appendicitis and its complications.

Objective: To determine the diagnostic accuracy of hyperbilirubinemia in diagnosing perforated appendix by taking per-operative findings as the gold standard.

Material & methods: It is a cross-sectional survey conducted at the Surgery department at PAF Hospital Mushaf, Sargodha. The duration of the study was from 1st June 2018 to 1st December 2018. A total of 160 patients of both gender with acute appendicitis with Alvarado Score ≥ 7 were included. Patients with age less than 12 years, HBsAg & anti-HCV positive, history of jaundice, history of liver disease (e.g.: Crigler-Najjar, Gilbert syndrome, cirrhosis, hepatitis), the patient is alcoholic, history of hemolytic disorders (e.g.: thalassemia, spherocytosis), history of the biliary disease (e.g.: biliary stones, worm infestation, atresia, etc), history of gastrointestinal& hepato-pancreato biliary malignancy, patient with appendicular mass per-operatively and appendectomy performed incidentally or for other indications were excluded. All patients were tested by routine laboratory investigations including LFTs hyperbilirubinemia was recorded. All cases underwent appendectomy by the same surgical team& peri-operative findings were recorded & compared with pre-operative total bilirubin levels. Patients were categorized as true positive, true negative, false positive & false negative.

Results: The age range in this study was from 12 to 60 years with a mean age of 35.231± 8.63 years and mean Pre-Op Bilirubin Levels was 0.812±0.72 mg/dl. Laboratory Findings (Bilirubin levels ≥ 1mg/dl) diagnosed 44(27.5%) patients and Per Operative Findings diagnosed 60(37.5%) patients with Perforated Appendix. Laboratory Findings (Bilirubin levels ≥ 1mg/dl) have shown a sensitivity of 50%, specificity of 86%, the diagnostic accuracy of 73%, PPV 68.18%, NPV 74.4%, (p=0.000) in the diagnosis of Perforated Appendix.

Conclusion: It is concluded that serum bilirubin level was higher in patients with appendiceal perforation, it s a definite predictive potential in these cases. Therefore, acquiring SB values upon admission can be used in combination with more recent diagnostic tests such as CT scans n, ultrasonography to help determine the presence of perforation and thus assist in timely clinical management.

Keywords: Perforated appendix, Hyperbilirubinemia, Diagnostic accuracy

INTRODUCTION

Acute appendicitis is an inflammation of the vermiform appendix. It is a disease of the young with 40% of cases diagnosed in the second and third decades of life in which the incidence is about 233/100,000 of the population [1]. The male to female ratio of 1.4 : 1 with a lifetime incidence of 8.6% & 6.7% respectively. It is the most frequent surgical emergency and the lifetime risk for an appendectomy is estimated to be 12% for males and 23% for females [2]. Often, it is challenging to reach a definite diagnosis, particularly in patients less than 3 years, pregnant, and older than 60 years of age. Diagnostic delay and timely treatment results in the increased rate of perforation, postoperative morbidity, mortality, and duration of hospital admission [1]. Young children have a higher rate of perforation with reported rates of 50-85% [3]. The mortality associated with simple appendicitis is reported to be 0.3% but increases to 6% in cases with perforation [2]. The aim of management includes early diagnosis and timely operative intervention to avoid complications like gangrene, perforation, and diffuse and generalized peritonitis.

Usually, the diagnosis is made based on clinical examination and raised leukocyte count (TLC). But in cases where clinical diagnosis is indeterminate, further evaluation by imaging. Despite the increased use of modern diagnostic modalities such as Sonography, computed tomography (CT), and, diagnostic laparoscopy, the rate of misdiagnosis of appendicitis has remained constant (15%) as has the rate of appendiceal rupture. In addition, these modalities have a number of significant limitations including cost, radiation exposure, operator dependency, availability, contrast agent allergy, false positive, false negative diagnosis, and, exposure to anaesthetics [1]. Diagnosis of acute appendicitis thus remains a surgical dilemma with perforation rates as high as 5-30% due to delayed surgical intervention.

Currently, several serum markers such as C-reactive protein (CRP), lactate an,d bilirubin have been proposed as a diagnostic tool for appendicitis. When compared CRP, TLC and lactate are found less specific than bilirubin as predictive markers for acute appendicitis and its complications, as these are general inflammatory markers, while the release of E. coli endotoxin affects bile flow makes bilirubin further specific (4).

The sensitivity and specificity for elevated bilirubin levels varied between 38% to 77% and 70% to 87% respectively. [2]

Two different studies showed elevated total bilirubin levels (>1mg/dl) in 38% of patients with perforated appendix[4]. As compared to the CRP level, hyperbilirubinemia had a specificity of 86% for appendiceal perforation or gangrene, compared with a specificity of only 35% for CRP [1]. Another study shows, as compared to CT scan, serum bilirubin level is less sensitive but more specific (96.9%) and it is easy and cheap investigation without any radiation hazard makes it a valuable adjunctive along with history and clinical examination in early diagnosis of appendiceal perforation.

Although international literature already exists for hyperbilirubinemia as a predictor of a perforated appendix, local data is still very inadequate in this context. Thus, this study is designed to determine the predictive potential of hyperbilirubinemia for the diagnosis of appendiceal perforation and should be used as an independent parameter in early diagnosis and reducing the morbidity and mortality associated with late diagnosis and delayed operative intervention in our population. This study will also add bulk to existing knowledge by providing statistics and comparing them with international data in the future.

Objective: To determine the diagnostic accuracy of hyperbilirubinemia in diagnosing perforated appendix by taking per-operative findings as the gold standard.

PATIENTS & METHODS

It is a cross-sectional survey done from 1st June 2018 to 1st December 2018 at the Surgery department PAF Hospital Mushaf, Sargodha. Patients (fulfilling our inclusion criteria) were incorporated into the study after taking informed consent. Patients aged 12 to 60 years of both genders diagnosed with acute appendicitis with an Alvarado score ≥ 7 were included. Patients with age less than 12 years, HBsAg & anti-HCV positive, history of jaundice, liver disease (e.g.: Crigler-Najjar, Gilbert syndrome, cirrhosis, hepatitis), history of hemolytic disorders (e.g.: thalassemia, spherocytosis), biliary disease (e.g.: biliary stones, worm infestation, atresia, etc), history of gastrointestinal or hepato-pancreato biliary malignancy, history of alcoholism or patients with appendicular mass per-operatively and those patients where appendectomy performed incidentally or for other indications were excluded from the study.

All patients fulfilling the inclusion criteria were enrolled. Their demographic information was recorded. All patients were informed about the aim of the study. Informed consent was taken. All patients were tested by routine laboratory investigations including LFTs hyperbilirubinemia was recorded. All cases underwent appendectomy by the same surgical team & per-operative findings were recorded & correlated with pre-operative total bilirubin levels. Patients were labeled as true positive, true negative, false positive & false negative. All information was collected through proforma.

True Positive= Cases with hyperbilirubinemia (≥ 1mg/dl) with positive perforation findings perioperatively.

True Negative= Cases bilirubin level < 1mg/dl with no perforation perioperatively.

False Positive= Cases with hyperbilirubinemia but no perforation findings perioperatively.

False Negative= Cases bilirubin level < 1mg/dl with positive perforation findings perioperatively.

Statistical analysis of data was done by using SPSS version 12. All the variables were identified. Demographic variables of the patients were analyzed by using simple descriptive statistics. Mean & Standard deviation was calculated for age and bilirubin levels. Frequency & percentages were determined for qualitative variables i.e., preoperative bilirubin level, the perforated appendix on lab findings & per-operative findings. A 2 x 2 contingency table was generated to calculate sensitivity, specificity, and positive & negative predictive values to determine the diagnostic accuracy of hyperbilirubinemia in the prediction of perforated appendicitis taking per-operative findings as the gold standard. Data was stratified for age, gender, and pre-op Alvarado score. Post-stratification chi-square test was applied, and p ≤0.05 was considered statistically significant.

RESULTS

The age range in this study was from 12 to 60 years with a mean age of 35.231± 8.63 years and mean preop Bilirubin Levels was 0.812±0.72 mg/dl. Laboratory Findings (Bilirubin levels ≥ 1mg/dl) diagnosed 44(27.5%) patients and peroperative findings diagnosed 60(37.5%) patients with a perforated appendix. Laboratory Findings (Bilirubin levels ≥ 1mg/dl) have shown a sensitivity of 50%, specificity of 86%, the diagnostic accuracy of 73%, PPV 68.18%, NPV 74.4%, (p=0.000) in the diagnosis of a perforated appendix. Stratification with respect to Alvarado Score of Laboratory Findings (Bilirubin levels ≥ 1mg/dl) versus Per Operative Findings are shown in Table-I & II

Table-1: Stratification with respect to Alvarado Score (7-8) of Laboratory Findings (Bilirubin levels ≥ 1mg/dl) versus Per Operative Findings(n=106)

Laboratory Findings (Bilirubin levels ≥ 1mg/dl)	Per Operative Findings		Total	P value
	Positive	Negative		
Positive	26 (TP)	30 (FP)	56	0.533
Negative	80 (FN)	76 (TN)	156	
Total	106	106	212	

Sensitivity:24.5%, Specificity:71.6%, DA=48.1%, PPV=46.4%, NPV= 48.7%

Table-2: Stratification with respect to Alvarado Score (>8) of Laboratory Findings (Bilirubin levels ≥ 1mg/dl) versus Per Operative Findings(n=54)

Laboratory Findings (Bilirubin levels ≥ 1mg/dl)	Per Operative Findings		Total	P value
	Positive	Negative		
Positive	18 (TP)	30 (FP)	48	0.020
Negative	36 (FN)	24 (TN)	60	
Total	54	54	108	

Sensitivity:33.3%, Specificity:44.4%, DA=38.9%, PPV= 37.5%, NPV=40%

DISCUSSION

In this study of 160 patients, hyperbilirubinemia was found in 44 of 60 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 no elevation or minimal elevation (<100 U/L) in ALT and AST in most of the cases. Similarly, ALP was either within the normal range or was minimal to moderately elevated. For gangrenous/perforated appendicitis, the P-value of SB was <0.000, sensitivity of 50%, specificity 86%, diagnostic accuracy by 73%, PPV 68.18%, NPV 74.4%, (p=0.000) in diagnosis of perforated appendix. The level of SB was higher than 3 mg/dL in cases of gangrenous/perforated appendicitis while in cases with acute appendicitis it was lower than 3 mg/dL (P<0.05). Generally, isolated hyperbilirubinemia was predominant in the majority of cases. These findings are almost similar to another reported study [5]. Since these findings were documented at the time of admission, it is unlikely that liver injury because of anaesthetic agents, blood transfusion, or medication was the cause of elevated bilirubin levels. The most likely reason of the rise in SB is therefore circulating endotoxemia as a result of appendiceal infection. Masaaki Akai et al [6] has shown hyperbilirubinemia occurs in systemic infections from various

disease, including peritonitis and systemic sepsis and there are several mechanisms leading to hyperbilirubinemia in systemic infection. Many bacterial infections have been demonstrated to induce cholestasis, in which E.coli and Bacteroides fragilis are most common primary causative organisms of appendicitis. E. coli endotoxins cause dose-dependent cholestasis and E. coli can also cause erythrocyte hemolysis, which increases the total bilirubin load. Furthermore, severe inflammation, as in complicated appendicitis, can cause edema of the intestine and that decreases intestinal motility, which can also induce cholestasis in patients with complicated appendicitis. These mechanisms may thus lead to hyperbilirubinemia in cases of acute appendicitis. It was demonstrated by Brinda in 2019 [8] that the underlying mechanism for hyperbilirubinemia is thought to be due to compromised appendix wall integrity that leads to translocation of bacteria and endotoxin into the portal system. This will disrupt the excretion of bilirubin into bile canaliculi. Serum total bilirubin increases as the infection becomes more severe. Pro-inflammatory cytokine and nitric oxide also play a role in triggering intrahepatic cholestasis. 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 oedema, elevated intraluminal pressure, and ischemic necrosis of mucosa, causing tissue gangrene and perforation. This process is associated with progressive bacterial invasion most likely facilitated by bacterial cytotoxins. The number of organisms isolated from patients with gangrenous appendicitis is five times greater than those with acute suppurative appendicitis. Estrada et al [11] 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. 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. Rarely free perforation of the appendix into the

peritoneal cavity occurs, which may be accompanied by peritonitis and septic shock and may be complicated by subsequent formation of multiple intraperitoneal abscesses. [12]. Two classical findings were described: firstly, simultaneous inflammation of the intestine (e.g., appendix), peritoneum and development of pyogenic liver abscesses, and secondly, bacteriological similarities of the gastrointestinal tract and pyogenic liver abscesses. These bacteria commonly reach liver from intra-abdominal organs, commonly from the appendix. Direct evidence of bacterial translocation from inflamed organs 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. These findings suggest that bacteria may transmigrate and produce portal bacteraemia, 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. In a study [6], hyperbilirubinemia, high CRP level, and fever may be useful predictors

of the severity of acute appendicitis, with hyperbilirubinemia being more useful among patients aged <65 years compared with older patients. CRP has higher sensitivity but lower specificity to appendicitis as compared to bilirubin.[13]. Thus, 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. This study shows that isolated hyperbilirubinemia without much elevation in the liver enzymes is a significant predictor of appendiceal perforation. This was demonstrated by a study by Estrada et al [11] and other studies [14,15] showing nearly a threefold risk of perforated appendicitis in patients with total bilirubin levels greater than 1 mg/dL. The other factors which were studied were age, gender and preop Alvarado score. P value was not significant in any of these criteria except age groups (31-60 years) (P=0.075). This finding is similar to other reported studies [11]. This study also shows that the Alvarado scoring system is also of great value with a significant P value and comparable sensitivity and specificity. Therefore, SB estimation, a simple economical 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.

CONCLUSION

It is determined that SB level was higher in patients with appendiceal perforation, it has a definite predictive potential in these cases. Therefore, obtaining SB values upon admission can be used in combination with more modern diagnostic tests such as CT scan, ultrasonography to help determine the presence of perforation and thus benefit in timely clinical management.

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