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Plasma total bilirubin levels in children with appendicitis admitted to the emergency department

Seref Selcuk Kilic[1], Mehmet Yigit[2]

[1] *Cukurova University, Faculty of Medicine, Department of Pediatric Surgery, Adana, Turkey*
[2] *University of Health Sciences, Department of Emergency Medicine, Haseki Research and Training Hospital, Istanbul, Turkey*

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Abstract
Appendicitis is one of the most common reasons for emergency abdominal surgery in children. Appendicitis patients have complaints that are common with many conditions and diseases. Therefore, early and accurate diagnosis of acute appendicitis is important in avoiding morbidity and associated complications. The aim of this study was to investigate the importance of hyperbilirubinemia in both the diagnosis of acute appendicitis and in distinguishing the severity of appendicitis in children. This retrospective study included 242 patients, 118 of whom had surgery for appendicitis and 124 who were admitted with suspected appendicitis between January 2011 and February 2015. Age, gender, preoperative plasma total bilirubin levels and pathological examination reports from patients' files were recorded. Patients with appendicitis were labelled as Group I. Patients with non-perforated appendicitis were in Group IA and patients with perforated appendicitis were in Group IB. Group II consisted of 124 patients who were hospitalized with suspected appendicitis but were discharged without an appendectomy. A statistically significant difference was observed between the two groups in terms of mean plasma total bilirubin levels (between group comparisons for Groups I and II, $p = 0.007$). According to the comparison of the subgroups with respect to the mean plasma total bilirubin levels, a statistically significant difference was not observed between subgroups IA and IB ($p = 0.770$).The present study indicates that plasma total bilirubin levels are not a reliable marker in either the diagnosis of appendicitis or the differentiation of perforated appendicitis from non-perforated appendicitis in children.

Keywords: Appendicitis, children, total bilirubin levels

Introduction

Appendicitis is the most frequent cause of emergent abdominal surgery in children. It is diagnosed in 1–8% of children who present to emergency rooms with abdominal pain and is most common in the second decade of life [1-3]. Clinical signs and symptoms of appendicitis are mostly nonspecific, and classical symptoms of appendicitis are not always present in children. Thus, an accurate diagnosis may be difficult and a delayed diagnosis may result in perforated appendicitis with associated complications. At the time of diagnosis, the rate of perforation is 26% in children [2]. An early diagnosis is crucial in decreasing morbidity and preventing further complications. However, no single sign, symptom, laboratory or radiological test will confirm the exact diagnosis of appendicitis.

Recent clinical studies investigating the relationship between hyperbilirubinemia and appendicitis indicate that hyperbilirubinemia may predict the diagnosis and severity of perforated appendicitis [4-14]. It is also well known that endotoxins of *Escherichia coli* and cytokines cause an increase in serum bilirubin levels in sepsis and intra-abdominal infections [15-16]. Therefore, E.coli may be initiate the increased levels of bilirubin in appendicitis cases.

This clinical study was designed to evaluate the significance of hyperbilirubinemia in diagnosing and determining the severity of appendicitis (perforated or non-perforated) in children.

Materials and Methods

Over a 48-month period from January 2011 through February 2015, 242 patients, 118 of whom required surgical management for appendicitis and 124 who were admitted for suspected appendicitis were enrolled in this retrospective clinical study.

Group I included patients who had undergone an operation for appendicitis (n = 118). Patients with non-perforated appendicitis were in Group IA and patients with perforated appendicitis were in Group IB. In Group II, there were 124 patients who were randomly selected out of 267 patients; these patients were hospitalized with the diagnosis of suspected appendicitis but discharged without an

***Coresponding Author:** Mehmet Yigit, University of Health Sciences, Department of Emergency Medicine, Haseki Research and Training Hospital, Istanbul, Turkey
E-mail: yigitacil@gmail.com

appendectomy. Appendicitis was confirmed by a pathological examination in Group I patients. Patients with a comorbidity were excluded from the study. Age, gender, preoperative plasma levels of total bilirubin and pathological examination reports obtained from patients' files and computer records were analyzed. A plasma bilirubin level above 1.2 mg/dl is defined as hyperbilirubinemia. Statistical analysis was performed with the IBM SPSS Statistics 19 software (IBM Corp., Armonk, NY, USA) computer program using the Chi-Square test and the Student's *t*-test.

Results

There were 71 (60.2%) male and 47 (39.8%) female patients with a mean age of 10.3 ± 2.7 years in Group I. Group II had 73 (58.9%) male and 51 (41.1%) female patients with a mean age of 9.9 ± 3.9 years. There were no statistically significant differences between groups in terms of age and gender, with significance values of $p = 0.37$ and $p = 0.74$, respectively.

Eleven patients in Group I (9.3%) and four patients (3.2%) in Group II had hyperbilirubinemia. Mean plasma total bilirubin levels in Group I and Group II were 0.81 ± 0.44 mg/dl and 0.63 ± 0.38 mg/dl, respectively. The difference between the groups was statistically significant ($p = 0.007$). A receiver operating characteristic (ROC) test was used to determine the significance of plasma total bilirubin levels in differentiating appendicitis from non-appendicitis and the area under the ROC curve (AUC) was 0.634.

Eight patients (9.1%) in Group IA and three patients (10%) in Group IB had hyperbilirubinemia. The mean plasma total bilirubin levels in Group IA and Group IB were 0.78 ± 0.44 mg/dl and 0.93 ± 0.43 mg/dl, respectively. The difference between groups was not statistically significant ($p = 0.77$). The ROC test was used to determine the significance of plasma total bilirubin levels in differentiating acute from perforated appendicitis and the AUC was 0.622. General characteristics of patients in Group I and II are shown in Table 1 and Table 2. Statistical analyses of plasma total bilirubin levels are shown in Table 3.

Discussion

Appendicitis is the most common cause for emergency abdominal surgery in children. Children with appendicitis generally present with abdominal pain. Nearly one third of patients with acute abdominal pain require admission for suspected appendicitis and 1–8% of these patients undergo an operation for appendicitis [1-3]. Right lower quadrant pain, nausea, vomiting, anorexia and focal tenderness or guarding in the right lower quadrant on physical examination strongly suggests appendicitis. However, only one third of the patients with appendicitis present with these classical signs and symptoms. A correct diagnosis is even harder in children less than five years of age who are unable to accurately describe their complaints. Laboratory and radiological examinations are unable to confirm an accurate diagnosis. Thus, the diagnosis of appendicitis is still a clinical challenge in children.

Early diagnosis is mandatory in order to prevent significant morbidity associated with perforated appendicitis. Potential complications associated with perforated appendicitis are wound infection, intra-abdominal abscess and injury to other intra-abdominal structures during surgery. Higher complication rates and the necessity for longer duration of antibiotic treatment lead to longer hospitalization and higher costs in patients with perforated appendicitis.

Recently, clinical data investigating the role of hyperbilirubinemia in the diagnosis and severity of appendicitis was published [4-14]. The plasma total bilirubin level increase associated with appendicitis is explained on the basis of infection and bacterial translocation. Increased bacterial load in appendicitis causes mucosal ulceration and bacterial translocation into the portal circulation [15]. *E. coli* in the portal circulation leads to hepatocellular injury and decreases the excretion of bile acids [16]. Intravascular bacteria may cause haemolysis [17]. Bacterial endotoxins and cytokines released secondary to bacterial translocation in intra-abdominal infections cause hepatocellular dysfunction [18]. Increased bacterial load in perforated appendicitis leads to higher levels of plasma bilirubin [19].

Recent data in the literature indicate that hyperbilirubinemia and/or plasma total bilirubin levels can be used as a marker to indicate appendicitis. Although, in our study, the mean plasma total bilirubin levels of patients with appendicitis were higher than in patients without appendicitis ($p = 0.007$), diagnostic performance of mean plasma total bilirubin level to distinguish appendicitis from non-appendicitis patients is evaluated with ROC test and had an AUC of only 0.634. An AUC value that is well below the guidelines of 0.75 and 0.99 cut offs for diagnosis and prognosis purposes is accepted in a poor test group in general interpretation [20-21]. In the present study, low AUC value of 0,634 in groups I and II reveal that mean plasma total bilirubin level has low discriminating power to diagnose appendicitis in children. Alternatively, differences between groups were not statistically different in terms of hyperbilirubinemia, and only 9.3% of children with appendicitis had hyperbilirubinemia. The mean plasma total bilirubin levels of patients in Group IA and Group IB were not statistically different ($p = 0.77$). According to the ROC analysis, the plasma total bilirubin levels were not a reliable marker in differentiating perforated appendicitis from non-perforated appendicitis (AUC = 0.622).

In conclusion, our data indicate that plasma total bilirubin levels are not a reliable marker in either the diagnosis of

appendicitis or the differentiation of perforated appendicitis from non-perforated appendicitis in children.

Table 1. Demographic and biochemical characteristics of patients in Group I

	Group I	Group IA	Group IB
Number	118	88 (74.6%)	30 (25.4%)
Age (year)	10.3 ± 2.7	10.3 ± 2,8	10.1 ± 2.4
Male	71 (60.2%)	52 (59.1%)	19 (63.3%)
Female	47 (39.8%)	36 (40.9%)	11 (36.7%)
Mean plasma total bilirubin level (mg/dl)	0.81 ± 0.44	0.78 ± 0.44	0.93 ± 0.43
Hyperbilirubinemia	11 (9.3%)	8 (9.1%)	3 (10%)

Table 2. Demographic and biochemical characteristics of patients in Group II

Group II	
Number	124
Age (year)	9.9 ± 3.9
Male	73 (58.9%)
Female	51 (41.1%)
Mean plasma total bilirubin level (mg/dl)	0.63 ± 0.38
Hyperbilirubinemia	4 (3.2%)

Table 3. Statistical analyses of plasma total bilirubin levels

	Group I and Group II	Group IA and Group IB
Sensitivity	9.46% %95 Cl	10.5% %95 Cl
Specificity	97.3% %95 Cl	90.9% %95 Cl
Positive Likelihood Ratio	3.5	1.1
Negative Likelihood Ratio	0.93	0.98
Odds ratio	3.7	1.1
AUC	0.634	0.622
P value	0.007	0.77

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