VOLUME-6 | ISSUE-4 | APRIL - 2017 • ISSN No 2277 - 8179 | IF : 4.176 | IC Value : 78.46

Original Research Paper

Hyperbilirubinemia and Procalcitonin as predictors of Appendiceal perforation: A Prospective Study

General Surgery

KEYWORDS: Hyperbilirubinemia, procalcitonin, acute abdomen, appendicular perforation.

Dr.Manav Dutta	Assistant professor,Dept of surgery SGRRIM and HS,Patel Nagar, Dehradun.
Dr.Anurag Bijalwan	Associate professor, Dept of surgery SGRRIM and HS,Patel Nagar, Dehradun.
Dr.Ratnanjali Mishra	Senior resident, Dept of surgery SGRRIM and HS,Patel Nagar, Dehradun.
Dr.Mirza Atif Beg	Associate professor, Dept of Pharmacology SGRRIM and HS, Patel Nagar, Dehradun.
Dr.Madhu Lata Rana	Associate professor, Dept of surgery SGRRIM and HS,Patel Nagar, Dehradun.

ABSTRACT

Background: Acute appendicitis is the most common cause of acute abdomen in surgical emergency and subsequent surgery. The diagnosis is essentially based on the clinical grounds and as a result misdiagnosis and delay in surgical intervention is a common and crucial problem. Diagnostic delay often result in appendicular perforation and peritonitis with increased complications. Serum bilirubin and serum Procalcitonin have been shown to increase in perforated appendicitis and therefore can be used as markers.

Aim: The purpose of this study is to evaluate the role of hyperbilirubinemia and raised serum Procalcitonin as predictors for appendiceal perforation or complicated appendicitis.

Materials and methods: This study consisted of patients admitted with the clinical suspicion of acute appendicitis. A total of 50 patients who had histologically proven appendicitis were included in the study. Subsequent to hospital admission all patients underwent thorough physical examination and routine laboratory investigations. The patients were grouped as simple acute appendicitis or complicated appendicitis (appendicular perforation and/or gangrenous appendicitis).

Results: Serum bilirubin and serum Procalcitonin were raised in a significant number of patients with complicated appendicitis. 17 of 20 patients with perforated appendicitis had bilirubin >1.5mg/dl (P<0.005). Sensitivity of serum bilirubin in predicting perforation was 85%, while specificity was 90%. 19 of 20 patients with perforated appendicitis had raised serum Procalcitonin levels (P<0.005). Sensitivity and specificity of serum Procalcitonin in predicting perforation was 95% and 83.33% respectively.

Conclusion: Bilirubin and Procalcitonin are important preoperative biochemical markers and are effective in predicting perforation in patients with acute appendicitis.

Introduction: Vermiform Appendix though described anatomically to be vestigial, is one of the most important surgically concerned organs in the human body. Acute appendicitis is essentially a clinical diagnosis supported by haematological and radiological investigation. It is a common inflammatory pathology in the right lower abdomen. Acute appendicitis is a common indication of abdominal surgery with a life time risk of 8.6% for males and 23.1% for females with a peak incidence between 10 to 30 years of age.[1] In elderly and paediatric age groups, clinical differentiation between complicated and uncomplicated acute appendicitis is difficult.[2,3] The goals of therapy in acute appendicitis is early diagnosis and prompt operative intervention, however this goal is not always accomplished since many patients do not seek medical attention in a timely manner and are at risk of developing complications like perforation, gangrene with its subsequent sequalae of increased morbidity. Post operative complications following open appendectomy are relatively uncommon and reflect the degree of peritonitis that was present at the time of operation and intraoperative spillage. Acute appendicitis and complicated appendicitis in particular has greater risk of post operative morbidity. The failure to differentiate between uncomplicated and perforated appendicitis may increase the mortality from 0.3% to 6%.[4] Among a vast array of serological markers for the diagnosis of acute surgical conditions, serum bilirubin and procalcitonin have been found as useful markers for appendiceal perforation in several studies.[5-12] Procalcitonin is an inactive precursor of calcitonin having 116 amino acid polypeptide glycoprotein. In normal metabolic conditions, It is found only in the C cells of the thyroid gland. **Assicot** has reported increased procalcitonin levels in patients with bacterial, fungal infections and sepsis.[13] In this study we investigated the role of bilirubin and procalcitonin in the diagnosis of perforation or complications in Acute appendicitis and recorded their sensitivity and specificity.

Materials and methods: This prospective study was carried out in the Departmentof Surgery, Shri Guru Ram Rai Institute of Medical & Health Sciences (SGRRIM&HS), Dehradun, over a period of 1 year from August 2015 to July 2016, after the approval from the Institutional Ethics Committee. Written informed consent was obtained from the patients/legal guardian after the full explanation of study protocol.

This study consisted of Patients admitted with a clinical suspicion of acute appendicitis. Most of the patients presented primarily to our institution and the rest of the patient were referred to us. The study finally included a group of those 50 patients who had histologically proven appendicitis and others were excluded. Patients who had history of liver disease or jaundice were also excluded from the study. Subsequent to hospital admission all patient underwent thorough physical examination and routine laboratory investigations. Pre-operative ultrasound was done. Clinical diagnosis was made based on medical history, physical and radiological examination as well as laboratory findings. Blood samples were taken immediately after admissions for measuring Procalcitonin, Serum Bilirubin (Procalcitonin Levels were measured by Procalcitonin Kit (VIDAS ® BRAHMS PCT-France). A Procalcitonin Level of >0.05ng/ml and bilirubin level of >1.5mg/dl was considered positive respectively. Elevated leukocyte count was also considered as a non specific marker of inflammation in the study. All appendicectomies were performed by conventional surgery and the specimens were sent for routine histo-pathological examination. The patients were grouped as simple acute appendicitis (Group 1), or complicated appendicitis (perforated appendicitis, gangrenous appendicitis, appendicular abscess) (Group 2).

Observation and Results: All patients included in the study underwent conventional open appendicectomy and specimens were verified by pathological examination.

Table 1 : Demographic Distribution

Age Group	No. of Patients
Up to 9 yrs	7

VOLUME-6 | ISSUE-4 | APRIL - 2017 • ISSN No 2277 - 8179 | IF : 4.176 | IC Value : 78.46

10-19yrs	25
20-29yrs	13
>30yrs	5
Total	50
Sex Distribution	
Males	20
Females	30

Table 2 : Duration of Pain

Hours	No. Of Patients	Percentage of Patients (%)
<24hrs	20	40
24-48	15	30
48-72	10	20
>72	05	10
Total	**50**	**100**

Out of the 50 patients included in this study, 20 cases turned out to be perforated appendicitis on intraoperative or histo-pathological findings. Serum bilirubin (Table 3) was elevated (>1.5) in 17 out of 20 patients of perforated appendicitis and 3 patients of non-perforated appendicitis had elevated serum bilirubin levels (>1.5). Sensitivity of serum bilirubin in predicting perforation was 85% while specificity was 90%. Positive predictive value of bilirubin for appendicular perforation was 85% and negative predictive value of bilirubin for appendicular perforation was 90%.

Serum bilirubin was > 1.5 mg\dl in significantly higher number of patients with perforated appendicitis in comparision to patients with non perforated appendicitis. Serum bilirubin is raised not only in perforated cases but also in simple cases of appendicitis. However rise in serum bilirubin level is more in perforated or gangrenous cases of appendicitis. The cut off value of 1.5mg/dl for bilirubin is an arbitrarily chosen value signifying that values above 1.5 mg/dl more often occur in cases of perforated of gangrenous appendicitis and values < 1.5 mg/dl occur more often in cases of simple appendicitis, therefore, few false negative and positive cases are expected to occur. False negative cases (03) might be explained by the possible decrease in counts of E. coli with i/v antibiotics before the hepatocytic microcirculatory compromise. False negative cases might also occur due to high threshold of RBC's to E. coli induced hemolysis.

Table 3: Serum Bilirubin Level

Status of Appendix	Bilirubin positive (>1.5mg/dl)	Bilirubin negative (<1.5mg/dl)	Sensitivity (%)	Specificity (%)
Perforated	17	3	85	90
Non Perforated	3	27		
Total	**20**	**30**		

The procalcitonin levels were raised in 19 patients out of 20 patients with perforated appendicitis, 5 patients with non-perforated appendicitis out of 30 patients were having increased levels of procalcitonin. The sensitivity and specificity of procalcitonin in predicting perforated appendicitis are 95% and 83% respectively. Positive predictive value of procalcitonin for appendicular perforation was 79.16% and negative predictive value of procalcitonin for appendicular perforation was 96.15%.

Table 4: Serum ProcalcitoninLevel

Status of Appendix	Procalcitonin positive (>0.05ng/ml)	Procalcitonin negative (<0.05ng/ml)	Sensitivity (%)	Specificity (%)
Perforated	19	1	95	83.33
Non Perforated	5	25		
Total	**24**	**26**		

Table 5:Leukocyte Count

Status of Appendix	Increased Leukocyte Count	Normal Leukocyte Count	Sensitivity (%)	Specificity (%)
Perforated	17	03	85	33.33
Non Perforated	20	10		
Total	37	13		

Discussion: Despite an array of newer diagnostic modalities in recent years, acute appendicitis continues to be a significant diagnostic problem. The diagnosis of acute appendicitis in most cases is based on clinical history and physical examination.[14,15] .The negative appendicectomy rate is relatively low in young male patients. The negative appendicectomy rate of 9 -20% has been reported in literature, while women of childbearing age, the figure may be as high as 30-50%. Many studies show that the rate of appendicular perforation (60 – 90%) is higher than negative appendicectomies in older age group, reflecting the difficulty in clinical diagnosis of acute appendicitis in older age group .[15,16] Diagnosis is also difficult during pregnancy and may result in both maternal and fetal mortality, as the incidence of perforation is usually proportional to the duration of the disease process. The morbidity and mortality rates associated with appendicitis are greatly increased when perforation ensues, wound infection rates may be increased, intra abdominal abscess formation increases 15 fold and mortality may be 50 times greater. Appendiceal perforation can also cause tubal infertility.[17] It is therefore obvious that the aim of the surgeon must be to prevent perforation. The most frequently used tests like leukocyte count and C- reactive protein for the diagnosis of acute appendicitis , although having an advantage of easy availability and low costs, are limited by low sensitivity and specificity . In our study leukocyte count was found to have 85% sensitivity and 33% specificity only.

Complicated perforated appendicitis and other septic conditions lead to increased procalcitonin and bilirubin which can act as their inflammatory markers. It was postulated that Procalcitonin might be a better marker for bacterial sepsis.[18] **Sand M et al** studied the diagnostic value of Procalcitonin in acute appendicitis.[8] They concluded that Procalcitonin was specially increased in patients with appendiceal perforation and gangrenous appendicitis. But it has a very low sensitivity, which prohibits its routine use for the diagnosis of acute appendicitis. Similar low sensitivity of 28% in acute appendicitis has also been reported by **Kouame DB**.[19] In our study sensitivity and specificity were 95% and 83.33% respectively. This study demonstrated that increase in Procalcitonin is statistically significant in patients with perforated appendicitis. Procalcitonin levels have been found to be lower in acute uncomplicated appendicitis compared to the other bacterial infections. The lower levels of procalcitonin in simple acute appendicitis can be explained by the insignificant bacterial translocation in uncomplicated cases. Similarly **Yamashita H et al** also found that procalcitonin was significantly higher in perforated appendicitis.[20,21]

In acute appendicitis, an ulceration of the mucosa in the appendix occurs due to the inflammation which facilitates bacterial translocation to the portal venous system. Appendix is most commonly infected by E.coli. When E.coli reaches the hepatic tissue through the portal venous system the bacteria interferes with the hepatocyte microcirculation, results in hepatic cell damage and compromises the excretion of the bile acids into the bile canaliculi.[22,23] Furthermore E.coli also induces intravascular hemolysis and both mechanisms may lead to an increased amount of serum bilirubin.[24] Bilirubin can be elevated in cases of sepsis, intra abdominal abscess from urological, gynaecological, gastro intestinal infections, antimicrobial therapy or in patients with genetic diseases such as Dubin Johnson syndrome, Rotors syndrome and Gilbert syndrome.[25] There exists no single diagnostic test or symptom, other than surgery with pathological examination, that can definitely result in a diagnosis. In our study the sensitivity and specificity of bilirubin in perforated appendicitis was 85% and 90% respectively. Similarly **Athahan K et al, Sand M et al** and **McGowan et al** also found that bilirubin was significantly higher in perforated appendicitis.[5, 10, 26] Our results showed that elevated serum Bilirubin and Procalcitonin can be considered as additional diagnostic tools

with Ultrasound and CT scans for the diagnosis of complicated appendicitis. Strength: Only histo-pathologically proven appendicitis cases were included in our study. Limitations: small sample size and no direct comparison with the standard diagnostic tools like, ultrasonography and/or CT scan of abdomen.

Conclusion: Our study results showed that Bilirubin and Procalcitonin are effective for differentiation of complicated from uncomplicated appendicitis. Bilirubin and Procalcitonin are important preoperative biochemical markers of complication in acute appendicitis, and can be a good predictor of complications,like perforation or gangrene in appendicitis. Their judicious use and interpretation can help in differentiating uncomplicated appendicitis (which can be managed conservatively) from complicated appendicitis (which require early surgical intervention). Multi center studies with larger sample size are required to substantiate our results.

Acknowledgement: Authors are thankful to all the staff members of surgery department and Operation Theater for their unconditional support to complete the study.

References -

1. AddisDG, Shaffer N, Fowler BS, Tauxe RV. The epidemiology of appendicitis and appendectomy in the United States.Am J Epidemiol. 1990;132:910–24.
2. Konan A, Hayran M, Kýlýç YA, Karakoç D, Kaynaroðlu V. Scoring systems in the diagnosis of acute appendicitis in the elderly. Ulus Travma Acil Cerrahi Derg 2011;17:396-400.
3. Escribá A, Gamell AM, Fernández Y, Quintillá JM, Cubells CL. Prospective validation of two systems of classification for the diagnosis of acute appendicitis. Pediatr Emerg Care 2011;27:165-69.
4. Sand M, Bechara FG, Holland –Letz T, Sand D, Mehnert G, Mann B. Diagnostic value of hyperbilirubinemia as a predictive factor for appendiceal perforation in acute appendicitis. Am j surg 2009;198:193-98.
5. McGowan DR, Sims HM, Shaikh I, Uheba M.The value of hyperbilirubinaemia in the diagnosis of acute appendicitis. Ann R Coll Surg Engl 2011;93(6):498.
6. Emmanuel A, Murchan P, Wilson I, Balfe P. The value of hyperbilirubinaemia in the diagnosis of acute appendicitis. Ann R Coll Surg Engl 2011;93:213-17.
7. Kafetzis DA, Velissariou IM, Nikolaides P, Sklavos M, Maktabi M, Spyridis G, Kafetzis DD, Androulakakis E. Procalcitonin as a predictor of severe appendicitis in children. Eur J Clin Microbiol InfectDis2005;24:484-87.
8. Sand M, Trullen XV, Bechara FG, Pala XF, Sand D, Landgrafe G, Mann B. A prospective bicenter study investigating the diagnostic value of procalcitonin in patients with acute appendicitis. Eur Surg Res 2009;43:291-97.
9. Yu CW, Juan LI, Wu MH, Shen CJ, Wu JY, Lee CC. Systematic review and meta-analysis of the diagnostic accuracy of procalcitonin, C-reactive protein and white blood cell count for suspected acute appendicitis. Br J Surg 2013;100:322-29.
10. Atahan K, Üreyen O, Aslan E, Deniz M, Çökmez A, Gür S, et al. Preoperative diagnostic role of hyperbilirubinaemia as a marker of appendix perforation. J Int Med Res 2011;39:609-18.
11. Estrada JJ, Petrosyan M, Barnhart J, Tao M, Sohn H, Towfigh S, et al. Hyperbilirubinemia in appendicitis: A new predictor of perforation. J Gastrointest Surg 2007;11:714-18.
12. Käser SA, Fankhauser G, Willi N, Maurer CA. C-reactive protein is superior to bilirubin for anticipation of perforation in acute appendicitis. Scand J Gastroenterol 2010;45:885-92.
13. Assicot M, Gendrel D, Carsin H, Raymond J, Guilbaud J, Bohuon C. High serum procalcitonin concentrations in patients with sepsis and infection. Lancet 1993;341:515- 18.
14. Abu-Yousef MM, Bleicher JJ, Maher JW, Urdaneta LF, Franken EA Jr, Metcalf AM. High-resolution sonography of acute appendicitis. AJR Am J Roentgenol 1987;149:53-58.
15. Adams DH, Fine C, Brooks DC. High-resolution real-time ultrasonography.A new tool in the diagnosis of acute appendicitis. Am J Surg 1988;155:93-97.
16. Jeffrey RB Jr, Laing FC, Lewis FR. Acute appendicitis: High-resolution real-time US findings. Radiology 1987;163:11-14.
17. Puylaert JB. Acute appendicitis: US evaluation using graded compression. Radiology 1986;158:355-60.
18. Hatherill M, Jones G, Lim E, Tibby SM, Murdoch IA. Procalcitonin aids diagnosis of adrenocortical failure. Lancet 1997;350:1749-50.
19. Kouame DB, Garrigue MA, Lardy H, Machet MC, Giraudeau B, Robert M. Is procalcitonin able to help in pediatric appendicitis diagnosis?. Ann Chir 2005;130:169-74.
20. Aslan A, Karaveli C, Ogunc D, Elpek O, Karaguzel G, Melikoglu M. Does noncomplicated acute appendicitis cause bacterial translocation?. Pediatr Surg Int 2007;23:555-58.
21. Yamashita H, Yuasa N, Takeuchi E et al. Diagnostic Value of procalcitionin for acute complicated appendicitis. Nagoya J Med Sci2016;78:79- 88.
22. Sisson RG, Ahlvin RC, Harlow MC. Superficial mucosal ulceration and the pathogenesis of acute appendicitis. Am J Surg 1971;122:378-80.
23. Rink RD, Kaelin CR, Giammara B, Fry DE.Effects of live Escherichia coli and Bacteroides fragilis on metabolism and hepatic pO2. Circ Shock 1981;8:601-11.
24. Shander A. Anemia in the critically ill. Crit Care Clin 2004;20:159-78.
25. Buyukasik Y, Akman U, Buyukasik NS, Goker H, Kilicarslan A, Shorbagi AI, et al. Evidence for higher red blood cell mass in persons with unconjugated hyperbilirubinemia and Gilbert's syndrome. Am J Med Sci 2008;335:115-19.
26. McGowan DR, Sims HM, Zia K, Uheba M, Shaikh IA.The value of biochemical markers in predicting a perforation in acute appendicitis. ANZ J Surg 2013;83:79-83.