



ORIGINAL RESEARCH PAPER

General Surgery

A PROSPECTIVE OBSERVATIONAL STUDY TO ASSESS ROLE OF ISOLATED HYPERBILIRUBINEMIA TO PREDICT GANGRENOUS/PERFORATED APPENDICITIS

KEY WORDS: Acute appendicitis, Gangrenous appendicitis, Perforated appendicitis, Hyperbilirubinemia.

Suresh Kumar Choudhary	Resident, SMS Medical College, Jaipur, Rajasthan, India, 302004.
Dinesh Kumar Bharti*	Associate Professor, SMS Medical College, Jaipur, Rajasthan, India, 302004. *Corresponding Author
Anupama Nagar	Consultant, Narayana Multispeciality hospital, Jaipur, Rajasthan, India.
Shalu Gupta	Professor, SMS Medical College, Jaipur, Rajasthan, India, 302004.
Saurav Kumar	Resident, SMS Medical College, Jaipur, Rajasthan, India, 302004.

ABSTRACT

Aim: The aim of study was to assess the role of hyperbilirubinemia as a predictor of gangrenous or perforated appendicitis.
Introduction: Appendicitis is characterised by means of infection and inflammation of the appendix. It was hypothesized that an association exists between the presence of appendiceal perforation and hyperbilirubinemia. The present study has been designed to evaluate the association between hyperbilirubinemia in cases of acute appendicitis and its complications.
Methods: This study was conducted at SMS hospital Jaipur as a prospective observational study. One hundred twenty patients of appendicitis were enrolled from 1 March 2017 to 30 November 2018 according sample size. Patients underwent appendectomy after confirmation of diagnosis by USG and other investigations and biopsy was sent for histopathological examination.
Results: Total 120 patients were analysed In our study as per inclusion criteria. Hyperbilirubinemia (>1.2 mg/dL) was found in gangrenous appendicitis and perforated appendicitis (91.67% and 100% respectively) as compared to in acute appendicitis (15.63%) cases (P<0.001). most of the acute (84.37%) and some gangrenous appendicitis (8.33%) patients had normal TSB but all perforated appendicitis patients had hyperbilirubinemia (>1.2 mg/dL). Liver enzymes were normal in most of cases or slightly elevated in some cases. Alvarado Score and CRP were also significantly elevated in complicated appendicitis than acute appendicitis.
Conclusion: Our study concluded that isolated hyperbilirubinemia is a predictor of perforated or gangrenous appendicitis. High Alvarado Score and CRP level are also indicating complicated appendicitis.

INTRODUCTION

Appendicitis is condition where the appendix become swollen, inflamed and filled with pus. The crude occurrence of acute appendicitis turned into 86 per 10000 in keeping with year¹. Perforated appendicitis occurred about at almost the equal prevalence in all sex and age. Appendicitis stays a lifetime risk of one in seven¹. For early and accurate preoperative detection, acute appendicitis stays an inexplicable challenge. There is not any dependable particular marker for acute appendicitis and is a reminder for the art of surgical diagnosis. In the continuing absence of a hundred percent correct investigation for appendicitis, any evaluation that could make a contribution to its diagnosis is treasured. Serum bilirubin may be a important marker for appendiceal perforation. It was hypothesized that an affiliation exists among the presence of appendiceal perforation and hyperbilirubinemia¹.

Portal blood brings nutritional and other stuff absorbed from gut which include bacteria and by-product (toxins) to the liver. In a small percentage even in healthy human, microbes are found in portal blood. It is generally cleared via detoxing and immunological action of reticuloendothelial (RES) system of liver that act as first line protection in clearing toxic stuff, micro organism and by-products. When microbes load overwhelms the Kupffer cellular function, it can cause dysfunction, deterioration or injury to hepatocytes and reflects elevation in serum bilirubin alone or combined with liver enzymes based on the sort, gravity and location Add of the injury.² Recently, additional materials known as Cytokines e.g. IL-6, Tumour necrosis factor, have also been labelled to be accountable of debilitated excretory task of liver and might cause increase in serum bilirubin level in the absence of elevated liver enzymes.

The relationship between the elevated serum bilirubin and

the variety of infectious disease has been recognised in some studies. This finding most mostly take place in neonates with gram negative bacterial infection and patients with intra-abdominal septicemia. The pathophysiology is contemplation to be because of bacteremia or endotoxemia inflicting impeded excretion of bilirubin from the bile canaliculi^{3,4}.

Some research have discovered bilirubin to be a helpful serological marker for anticipation of acute and complicated appendicitis⁵⁻⁶.

The current study has been designed to assess the association between hyperbilirubinemia in cases of acute appendicitis and its complications.

The stress has been to establish a probable role of hyperbilirubinemia to predict of gangrenous perforated appendicitis so that serum bilirubin level upon admission may be used in conjunction with other diagnostic tests as such as CT scan and USG to assist decide the presence of perforation of appendix and use full resource in proper clinical management.

MATERIALS & METHODS

It was a prospective observational study, conducted at Department of General Surgery, SMS Medical College, Jaipur from 1 March 2017 to 30 November 2018 and 120 patients of appendicitis were enrolled as per sample size and inclusion criteria. Inclusion criteria were patients of 15 years of age and above, cases of acute appendicitis admitted and underwent for surgery in department of surgery and cases giving written informed consent. Exclusion criteria were appendectomy performed incidentally or for other indications, all other past and concurrent diseases which derange liver functions

except appendicitis and all other cases of hyperbilirubinemia.

Approval of the institutional ethical committee was taken to conduct the above study. Informed consent was taken. After history and clinical examination, patient underwent USG whole abdomen or CT abdomen. After that patient underwent routine blood investigations including, serum bilirubin. Appendicitis was diagnosed after complete evaluation. Alvarado score was calculated. Patients underwent appendectomy and biopsy was sent for histopathological examination. In current study, patients were categorized in three groups as: Group A= Acute appendicitis, Group G= Gangrenous appendicitis, Group P= Perforated appendicitis. Normal reference values of TSB (1.2 mg/dl), ALT (≤ 50 U/L), AST (≤ 50 U/L) and ALP (15-300 U/L) were taken as per institute laboratory standard values.

STATISTICAL ANALYSIS

Continuous variables are presented as mean \pm SD, and categorical variables are presented as absolute numbers and percentage. Data will checked for normality before statistical analysis. Normally distributed continuous variables will be compared using the unpaired t test, whereas the Mann Whitney U test will be used for those variables that are not normally distributed. Categorical variables will be analyzed using either the chi square test or Fisher's exact test. For all statistical tests, a P value less than 0.05 will be considered statistically significant.

RESULTS-

Acute, gangrenous and perforated appendicitis found in 64 (54.33%), 12 (10.00%) and 44 (36.67%) patients respectively on final histopathological examination. Mean age of all patients was 25.88 ± 10.13 years. 61 (49.17%) cases were male and 59 (50.83%) female. Mean duration of symptoms and hospital stay were 3.85 ± 2.51 and 3.38 ± 1.1895 days. Mean TLC was 12.18 ± 5.08 cu.mm.

Mean total serum bilirubin (TSB) was 1.30 ± 0.52 mg/dL in all group patients. Raised TSB found in 65 (54.17%) patients. Mean TSB were 0.94 ± 0.33 mg/dL, 1.85 ± 0.56 mg/dL and 1.67 ± 0.32 mg/dL in Group A, Group G and Group P respectively. Group G and P ($P < 0.001$) had significantly higher TSB than Group A. Hyperbilirubinemia was observed in 15.63%, 91.67%, 100% patients in group A, G and P, respectively ($P < 0.001$). TSB is Shown in table no. 1 & 2.

Table 1- TSB, AST, ALT and ALP

TSB (mg/dL)	Total number of patients (n=120)	Mean	P value	A vs. G	A vs. P	G vs. P
	Group A (n=64)	0.94 ± 0.33	< 0.001	< 0.001	< 0.001	0.272
	Group G (n=12)	1.85 ± 0.56				
	Group P (n=44)	1.67 ± 0.32				
	Mean TSB in all patients (n=120) = 1.30 ± 0.52 mg/dL					
AST (U/L)	Group A (n=64)	32.25 ± 19.74	0.524	0.33	0.969	0.28
	Group G (n=12)	38.92 ± 39.13				
	Group P (n=44)	31.27 ± 14.81				
	Mean AST in all patients (n=120)	33.56 ± 21.30 U/L				

ALT (U/L)	Group A (n=64)	29.27 ± 19.96	0.290	0.004	0.949	0.003
	Group G (n=12)	47.50 ± 26.02				
	Group P (n=44)	28.20 ± 8.82				
	Mean ALT in all patients (n=120)	30.70 ± 18.26 U/L				
ALP (U/L)	Group A (n=64)	72.67 ± 70.38	0.290	0.56	0.4	0.988
	Group G (n=12)	52.67 ± 24.59				
	Group P (n=44)	59.02 ± 17.92				
	Mean ALP in all patients (n=120)	65.67 ± 53.43 U/L				

mean \pm 1 SD, Number, or p-value: < 0.05 (significant). Abbreviations: TSB, total serum bilirubin; AST, Aspartate aminotransferase; ALT, alanine aminotransferase; ALP, serum Alkaline phosphatase.

Table 2- Distribution of the cases according to Total S. Bilirubin (TSB)

Total number of patients (n=120)	TSB (mg/dL)	
	≤ 1.2 (n=55)	> 1.2 (n=65)
Group A (n=64)	54 (84.37%)	10 (15.63%)
Group G (n=12)	1 (8.33%)	11 (91.67%)
Group P (n=44)	0 (0.00%)	44 (100.00%)

Number (%)

Mean AST and ALT of all groups patients were 33.56 ± 21.30 and 30.70 ± 18.26 U/L. Mean AST and ALT in Group A, G and P were 32.25 ± 19.74 & 29.27 ± 19.96 , 38.92 ± 39.13 & 47.50 ± 26.02 U/L and 31.27 ± 14.81 & 28.20 ± 8.82 U/L. AST and ALT were comparable in all group (P value = 0.524, 0.290). AST and ALT are Shown in table no. 1.

Mean ALP of all groups patients was 65.67 ± 53.43 U/L. Mean ALP of group A, G and P were 72.67 ± 70.38 , 52.67 ± 24.59 and 59.02 ± 17.92 U/L respectively. ALP was comparable in all group (P value = 0.29). ALP is Shown in table no. 1.

Mean Alvarado Score was 7.86 ± 2.04 in all groups. Mean Alvarado Score was 6.86 ± 2.21 , 8.75 ± 0.97 and 9.07 ± 0.95 Group A, Group G and Group P respectively. Alvarado Score was found significantly higher in Group G ($P = 0.002$) and P ($P = 0.000$) than Group A.

The area under the curve was found 0.853 for TSB. A 1.250 UNIT area under the curve (AUC = 0.853) optimal cut-off value of TSB, with a sensitivity of 100.0% and a specificity of 72.4%, was determined with SE 0.036. This level is excellent to use as a screening test. ROC curve analysis for CRP is shown in figure no 1

ROC curve analysis to find out the optimal cutoff value of S. Bilirubin in complicated appendicitis (perforated and gangrenous) vs. acute appendicitis without complication.

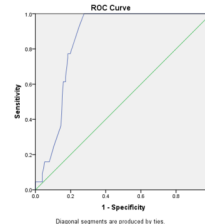


Figure 1- Graph 1. ROC curve analysis

ROC curve analysis was performed to determine the optimal cut-off values of significant variables (CRP) detected between the two groups. A 6.15 mg/L area under the curve (AUC = 0.802) optimal cut- off value of CRP, with a sensitivity of 100.0 % and a specificity of 54 %, was determined with SE 0.039. ROC curve analysis for CRP is shown in figure no. 2.

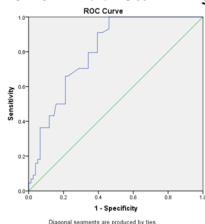


Figure 2-

Acute, gangrenous and perforated appendicitis were diagnosed in 64 (54.33%), 12 (10.00%) and 44 (36.67%) patients respectively on the basis of histopathological examination.

DISCUSSION

This study was conducted to predict complicated appendicitis by TSB, age total leucocyte count, Alvarado score and C-reactive protein. TSB was raised in 65 (54.17%) cases whereas 55 (45.83%) cases had normal TSB level. Mean TSB was 1.85±0.56 mg/dL and 1.67±0.32 mg/dL of gangrenous appendicitis and perforated appendicitis respectively. TSB was significantly elevated in gangrenous and perforated appendix than those in acute appendicitis (P<0.001). In present study, significant hyperbilirubinemia was observed in gangrenous and perforated appendicitis (100% and 15.63%, respectively) as compared to acute appendicitis (15.63%) cases (P <0.001). Most of acute (84.67%) and some gangrenous (8.33%) appendicitis patients had normal value of TSB, but all perforated appendicitis patients had hyperbilirubinemia. This hyper bilirubinemia was mixed in type (both conjugated and non-conjugated) in most of the patients. Hyperbilirubinemia is a predictor of complicated appendicitis, similar to previous studies as follows. Chaudhary P et al. (2013)¹⁰ analysed 50 patients of appendicitis and they found hyperbilirubinemia in 30 out of 42 patients of acute suppurative appendicitis and all gangrenous or perforated appendicitis. TSB was more elevated in gangrenous and perforated appendix than those in acute appendicitis (P<0.001). Souza ND et al. (2013) found, significant hyperbilirubinaemia was associated with perforated appendicitis than simple appendicitis (p <0.0001)¹¹. In 2011, McGowan DR et al. found that a perforation had increased bilirubin levels (p<0.001) compared with non-perforated appendicitis, with a specificity of 88.3% of bilirubin >21µmol/l⁶.

All preceding studies aid the effect of present study that isolated hyperbilirubinemia in complicated appendicitis. Since isolated hyperbilirubinemia was documented at the time of admission. Most likely explanation of rise in serum bilirubin is circulating endotoxemia as a result of appendicular infection. Utili et al. have 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 is possible that E.coli endotoxin exerts direct damage at the cholangiolar level¹¹⁻¹⁴.

Mean AST/SGOT was 32.25±19.74U/L, 38.92±39.13U/L and 31.27±14.81U/L in acute appendicitis, gangrenous appendicitis and perforated appendicitis respectively. Mean ALT was 29.27±19.96U/L, 47.50±26.02U/L and 28.20±8.82U/L in acute, gangrenous and perforated appendicitis respectively. ALP was 2.67±70.38 U/L, 52.67±24.59 U/L and 59.02±17.92 U/L in acute, gangrenous and perforated appendicitis respectively. In the present study AST (P value = 0.524), ALT (P value = 0.290) and ALP (P value =

0.29) were comparable in all groups which were similar of results of studies Chaudhary P et al. (2013)¹⁰ and they found a normal or minimal elevation in ALT, AST and ALP in most of the cases.

Mean Alvarado Score was 6.86±2.21, 8.75±0.97 and 9.07±0.95 in acute appendicitis, gangrenous appendicitis and perforated appendicitis respectively. A significant difference was observed according to Alvarado Score on the ANOVA test (P=.000). On applying post Hoc Analysis to find the mean difference in the two groups separately, Alvarado Score was significantly higher in gangrenous appendicitis (P=.002) and perforated appendicitis (P=.000) as compared to acute appendicitis patients which were alike to Ghag GS et al. (2016)¹⁵ study. They found 40% and 56.66% of the patients have the Alvarado score 6 or 7 and 8 or 9 in acute, gangrenous and perforated appendicitis respectively (p value 0.038). They concluded a high Alvarado Score indicates complicated, perforated appendicitis.²⁴ Our results are also comparable to those reported by Dey S¹⁶, Jawaid A¹⁷, Baidya N¹⁸, Chan MY¹⁹, and Khan I²⁰.

The positive predictive value of TSB was 98.21% and CRP was 100%, which is nearly similar to the study by S. Khan (2008)²¹. The negative predictive value of TSB was 84.61% in our study as compared to 100% in the study by Chaudhary P (2013)¹⁰. The negative predictive value of CRP was 61.54% in our study. Therefore, in suspected cases of appendicitis, the elevation of TSB and CRP can be used as a criterion to diagnose and manage acute appendicitis. On the other hand, in clinically suspected cases of acute appendicitis normal TSB and CRP does not exclude the diagnosis of acute appendicitis as the negative predictive value of these parameters is significant.

Our study strengths were adequate sample size, statically sound and prospective study. Lacunae of our study were a single centre study and it is not an RCT study. Therefore, TSB estimation, being a simple, cheap and easily available test in every laboratory can be added to the routine investigation list of clinically suspected cases of acute appendicitis for the confirmation of diagnosis. Since the rise in TSB was significantly higher in patients with complicated appendicitis like the perforated or gangrenous appendix, it has definite predictive potential in these cases.

Therefore, obtaining serum bilirubin values upon admission can be used in conjunction with more modern diagnostic tests such as CT scan, ultrasonography to help determine the presence of perforated or gangrenous appendicitis and thus aid in prompt clinical management.

CONCLUSION

Our study concluded that isolated hyperbilirubinemia (total serum bilirubin level >1.2mg/dl) without much elevation in liver enzymes had a predictive potential for the diagnosis of gangrenous and perforated appendicitis with 100% of sensitivity and 98.21% positive predictive value. Serum bilirubin along with imaging is helps predict perforated or gangrenous appendicitis and in planning early surgical management.

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