ISSN Print: 2394-7500
ISSN Online: 2394-5869
Impact Factor: 8.4
IJAR 2021; 7(7): 101-104
www.allresearchjournal.com
Received: 21-04-2021
Accepted: 05-06-2021

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Hyperbilirubinemia as a predictor of gangrenous/perforated appendicitis: A prospective study

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Abstract
Background: Appendicitis is one of the commonest causes of abdominal pain requiring emergency surgery. Often, it is difficult to reach a proper diagnosis. There may not be classical symptoms and signs of appendicitis. Different clinical signs and symptoms always mimic the diagnosis of acute appendicitis, as there are a number of causes leading to pain in right iliac fossa particularly in female patients. Diagnosing acute appendicitis clinically still remains a common surgical problem. Accurate diagnosis can be aided by additional testing or expectant management or both. These might delay laparotomy and lead to appendiceal perforation with increased morbidity and hospital stay [1-2].
Hyperbilirubinemia is a new diagnostic tool for perforation of appendix. Hyperbilirubinemia is the result of imbalance between production and excretion of bilirubin by the liver. The present study has been designed to evaluate the association between hyperbilirubinemia in cases of Gangrenous/ perforated appendix.
Method: The study was done at our tertiary care centre in the department of General Surgery, Dr. D. Y. Patil. Medical College, Pimpri, Pune on attending OPD/IPD after due permission from the Institutional Ethics Committee and Review Board and after taking Written Informed Consent from the patients.
Inclusion criteria for the study was as follows: male or female cases of 15 years of age and above till the age of 75years with a prelim diagnosis of acute appendicitis posted for an appendectomy at of our hospital.
Exclusion criteria was as follow: Incidental appendectomy or for other indications; cases who were under 15 years of age; cases with a already radiologically diagnosed lump appendix; known documented history of ALD; any other liver or heamolytic disease which is associated with HB; known case of a GI or hepatopancreatobiliary malignancy.
Quantitative data is presented with the help of Mean and Standard deviation. Comparison among the study groups is done with the help of unpaired t test as per results of normality test. Qualitative data is presented with the help of frequency and percentage table. Association among the study groups is assessed with the help of Fisher test, student 't' test and Chi-Square test. 'p' value less than 0.05 is taken as significant.
Results: The incidence of perforated/gangrenous appendix was 24% in our study. 75% patient with Gangrenous/perforated appendix had elevated bilirubin levels while10.5% with acute appendicitis had elevated bilirubin levels. a sensitivity of 72.22%, specificity of 85.71% while PPV and NPV were 92.86% and 54.55% respectively.
Conclusions: Total serum bilirubin levels as a part of Liver function test profile estimation has been a routinely used and is easily available, also an affordable test available in every laboratory. As our study suggest the rise in serum bilirubin levels were considerably higher in cases with perforation hence it has a clear differential along with predictive potential. With the aid of serum bilirubin levels as an indication of perforated appendix a prompt and planned and premeditated clinical management can be initiated.

Keywords: Hyperbilirubinemia, gangrenous/perforated, emergency surgery

Introduction
Sudden or acute abdominal discomfort and pain are a common presentation in the emergency department. One of the most common reason behind acute abdominal pain is acute appendicitis the treatment and diagnosis of which has radically changed over the few last decades.

In the past appendicitis was diagnosed solely based on clinical acumen of presenting signs and symptoms but in recent years diagnosis also consists of inflammatory laboratory values and indicators such as leukocytes, neutrophils, and CRP [1-3].

The life time rate of a probable appendectomy is twelve percent for males and twenty five percent for females [4]. it is common presentation in childhood & early adult life and rare in infants. Peak incidence is reached in the late teens & early 20s. Appendicular luminal obstruction is necessary for the inflammation to occur, obstruction either by a fecolith or stricture is found in most of the cases. Pathogenesis of inflammation remains unknown in a few cases with no luminal obstruction.

Significant risk of morbidity and mortality is associated with Perforation of gangrenous appendix. 25.8% of the total cases of appendicitis end up with a perforated appendix. Fecoliths are found nearly in 90% of the patients with acute gangrenous appendicitis with rupture.

Hyperbilirubinemia now is being evaluated as a new diagnostic indicator for a gangrenous/perforated appendix. Etiology varies from hepatocellular, hemolytic or cholestatic pathologies. Bacteria and its product (toxins) get absorbed by portal blood and carried to the liver. It is generally excreted or cleared by the action of the reticuloendothelial system present in the liver. RE behaves as the first-line defense in tackling with bacteria and their endotoxins but overwhelming of the Kupffer cell function due to bacterial overload can lead to damage and dysfunction of the hepatocytes in the liver parenchyma. It results in a rise in TSB alone or along with liver enzymes depending severity of the lesion.

the founding of a promising part of HB being considered as a predictor of gangrenous/perforated appendicitis has been stressed in this study so that total serum bilirubin levels at admission which can assist determine the diagnosis of perforation and lead to an early diagnosis and treatment. A secure, cost effective, fast, easily available and precise diagnostic indicator for appendicitis is the given necessity of the time.

Hence the current study was done at Dr. D. Y. Patil medical college and research Centre, Pune to evaluate raised serum bilirubin levels as a predictor of perforated/gangrenous appendix.

Methods

Study Type

A hospital based prospective study was conducted with 50 patients to evaluate the association between hyperbilirubinemia in cases of appendicular perforation.

Study Setting

The present study was conducted on clinically diagnosed cases of acute appendicitis coming to the Dept. of Surgery, Dr. D. Y. Patil Medical College, Hospital and Research Centre, Pimpri, Pune.

Study Period

The period of data collection was spread over one and half year months from October 2018 to March 2020.

Sampling Method & Sample Size

50 patients of features suggestive of acute appendicitis to demonstrate a hyperbillirubin as a marker for perforated/ gangrenous appendix. Who fulfilled the inclusion criteria. Patients were included in the study after taking their voluntary informed consent.

Study subjects

Inclusion criteria

1. All patient between age of 15-70 years of age
2. All Patient clinically presenting as acute appendicitis.

Exclusion criteria

1. All patients documented to have history of jaundice and liver disease
2. All patient to have chronic alcoholism
3. Haemolytic diseases
4. All patient with acquired or congenital biliary diseases, hbsag positive, hepatobiliary carcinoma, choliathiasis.
5. All patient diagnosed with appendicular lump
6. Age above 75yr or below 15yr
7. Immunocompromised patients.

Statistial Analysis

Quantitative data is presented with the help of Mean and Standard deviation. Comparison among the study groups is done with the help of unpaired t test as per results of normality test. Qualitative data is presented with the help of frequency and percentage table. Association among the study groups is assessed with the help of Fisher test, student 't' test and Chi-Square test. 'p' value less than 0.05 is taken as significant**.**

Results

Distribution of patients according to Age

Majority of the patients (48%) were in the age group of 15-20 years followed by 21-30 years (22%).

Age (years)	N	%
15-20 years	24	48%
21-30 years	11	22%
31-40 years	3	6%
41-50 years	9	18%
51-60 years	2	4%
61-70 years	1	2%
Total	50	100%
Mean ± SD	27.84 ± 12.93	

Distribution of patients according to Incidence of Gangrenous/Perforated Appendix

The incidence of gangrenous/perforated appendix in clinical cases of acute appendicitis was 24% in our study.

Gangrenous/Perforated Appendix	N	%
Yes	12	24%
No	38	76%
Total	50	100%

Association of Gangrenous/Perforated Appendix and Serum Bilirubin Levels in patients

9 of the 12 patients (75%) with Gangrenous/perforated appendix had elevated bilirubin levels while 4 of the 38 patients (10.5%) with acute appendicitis had elevated bilirubin levels. Significantly higher number of patients with Gangrenous/perforated appendix had elevated bilirubin levels as per Chi-square test ($p<0.05$).

Serum Bilirubin Levels	Gangrenous/Perforated Appendix						p Value
	Yes		No		Total		
	N	%	N	%	N	%	
Raised	9	75%	4	10.5%	13	26%	<0.05
Normal	3	25%	34	89.5%	37	74%	
Total	12	100%	38	100%	50	100%	

Sensitivity, Specificity and Accuracy of hyperbilirubinemia in predicting Gangrenous/ perforated appendix

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Hyperbilirubinemia	72.22%	85.71%	92.86%	54.55%	78.64%

Comparison of patients with and without Gangrenous/perforated appendix

It was observed that the patients with Gangrenous/perforated appendix had significantly elevated serum bilirubin levels (1.21 ± 0.67mg/dl vs. 3.11 ± 1.56mg/dl).

Parameters	Acute appendicitis		Gangrenous/Perforated appendix		p Value
	N	%	N	%	
Age (years)	27.55 ± 13.08		28.75 ± 12.97		>0.05
Sex					
Male	25	50%	9	18%	>0.05
Female	13	26%	3	6%	
Parameters					
Hb (g/dL)	14.24 ± 1.72		13.75 ± 0.75		>0.05
TLC (cell/mm^3)	11548.66 ± 4628.89		11687.08 ± 5241.62		>0.05
Serum Bilirubin (mg/dl)	1.21 ± 0.67		3.11 ± 1.56		<0.05
AST (U/L)	28.89 ± 21.24		30.67 ± 9.92		>0.05
ALT (U/L)	35.05 ± 12.71		47.25 ± 15.90		<0.05
ALP (U/L)	177.42 ± 7.95		189.25 ± 24.92		>0.05
CRP (mg/L)	105.13 ± 22.77		166.33 ± 8.99		<0.05
Alvarado Score	8.24 ± 1.38		8.17 ± 1.75		>0.05
Duration of Symptoms	2.39 ± 1.22		2.58 ± 1.51		>0.05

Discussion

In the present study, majority of the patients (48%) were in the age group of 15-20 years followed by 21-30 years (22%), 41-50 years (18%), 31-40 years (6%), 51-60 years (4%) and 61-70 years (2%). The mean age of the patients was 27.84 ± 12.93 years. 34 (64%) patients were male while 16 (32%) patients were female. There was male preponderance and the M:F ratio was 2.12:1. This is similar to the studies of Chaudhary P *et al.* [7], Vineed S *et al.* [86] and Syed Raj R [74].

It was observed in the present study that the mean Haemoglobin (Hb) level of patients was 14.12±1.55g/dL while the mean total leukocyte count (TLC) and serum bilirubin was 11581.88±4727.65 cell/mm^3 and 1.66±1.25mg/dl respectively. The mean Aspartate Aminotransferase (AST) and mean Alanine Aminotransferase (ALT) was 29.32±19.06U/L and 37.98±14.36U/L respectively while the mean Alkaline Phosphatase (ALP) and C-reactive protein (CRP) was 180.26±14.60U/L and 119.82±33.27mg/L respectively. This is comparable to the studies of Syed Raj R [74], Chaudhary P *et al.* [7] and Vineed S *et al.* [86].

The incidence of perforated appendix was 24% in our study. This is concordant to the studies of Chaudhary P *et al.* [7] and Vineed S *et al.* [86]. Prospective study found 5 (10%) cases had perforated appendix. Vineed S *et al.* [86] prospective study found out of the twenty percent of patient Intra-operatively had perforated appendix.

It was observed in our study that raised serum bilirubin level (>1.2 mg/dl) was reported in 13 (26%) patients and normal in 37 (74%) patients. This is consistent with the studies of Chaudhary P *et al.* [7], Vineed S *et al.* [86], Syed Raj R [74] and Gopalreddy D *et al.* [76].

It was observed in our study that 9 of the 12 patients (75%) with perforated appendix had elevated bilirubin levels while 4 of the 38 patients (10.5%) with acute appendicitis had elevated bilirubin levels. Significantly higher number of patients with perforated appendix had elevated bilirubin levels as per Chi-square test (p<0.05). This finding was consistent with the studies of D'Souza N *et al.* [57], Chaudhary P *et al.* [7] and Vineed S *et al.* [86].

D'Souza N *et al.* [57] single centre, prospective observational study assessing diagnostic value of bilirubin in perforated vs simple appendicitis reported that appendicitis has a significant association with hyperbilirubinaemia. Vineed S *et al.* [86] prospective study reported a raised TSB values of ninenteen cases out of twenty nine cases of complicated appendicitis and just nine of seventy one cases of uncomplicated appendicitis.

This excess of bacterial load in cases of perforated appendix reaches the portal circulation leading to the hepatic parenchyma and hinder with the bilirubin secretion. The pro inflammatory factors as discussed before are the major etiology in the interference of bilirubin secretion [78, 85].

It was observed in the present study that the patients with perforated appendix had significantly elevated serum bilirubin levels (1.21 ± 0.67mg/dl vs. 3.11 ± 1.56mg/dl). This is comparable to the studies of Chaudhary P *et al.* [7], D'Souza N *et al.* [57], Gopalreddy D *et al.* [76], Syed Raj R [74] and Akai M *et al.* [75].

Acknowledgement

First and foremost I would like to like to offer my deepest appreciation to my guide Dr. Shivmurti Khandalkar, Professor, Department of general surgery. for his constant support, guidance, enthusiasm and wisdom. I would also

like to express my gratitude for my head of unit Dr (Mrs) D S Nirhale, Professor & HOU, Department of general surgery. This wouldn't have been possible without your support, encouragement, patience and guidance.
I would also like to express my deepest gratitude Dr. Shahaji Chavan, Head of department, general Surgery for his support and guidance in seeing this project through completion. I take this golden opportunity to show my indebtedness to my institution, Dr. D. Y. Patil Medical College, Pimpri, Pune. Finally, my special thanks to all the patients without whom this dissertation would not have been successful.

Declarations

Funding: Nil
Conflict of interest: No conflicts
Ethical approval: Obtained

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