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Original article

Evaluation of hyperbilirubinemia in acute inflammation of appendix: A prospective study of 45 cases

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Abstract

Background: Hyperbilirubinemia is the result of imbalance between production and excretion of bilirubin by the liver. It may be because of hepatocellular, cholestatic or haemolytic diseases. Liver receives blood mainly through portal venous system, which receives blood from abdominal organs. Portal blood carries nutrients and other substances absorbed from gut including bacteria and its product (toxins). In small percentage, even in normal healthy people, bacteria are found in portal blood. It is commonly cleared by detoxification and immunological action of reticuloendothelial (RES) system of liver that act as first line defence in clearing toxic substances, bacteria and it's products. But when bacterial load overwhelms the Kuffer cell function, may cause dysfunction or damage to the hepatocytes (liver parenchyma). It reflects, rise in serum bilirubin (SB) alone or in combination with liver enzymes depending upon the type, severity and site of lesion. Recently, another substance known as Cytokines e.g. IL-6, Tumour necrosis factor (TNF), have also been labelled to be responsible for depressed excretory function of liver and may lead to increase in SB level without rise in liver enzymes.

Aim: To evaluate hyperbilirubinemia associated in acute inflammation of appendix (acute appendicitis and its complication).

Material and methods: This is a prospective study conducted at NGMC Teaching hospital Nepalgunj, Nepal during Oct.2004-Oct.2005. 45 Consecutive cases of acute appendicitis admitted in surgical unit III, were recruited for this study. Clinically suspected cases were subjected to investigations to confirm the diagnosis. Investigations included total leucocytes count, differential leucocytes count, urine analysis and ultrasound. These cases were also subjected to routine liver function tests. Subsequently these cases were operated and clinical diagnosis was confirmed per–operatively and post operatively by histopathological examination of the specimen. Their clinical and investigative data were compiled and analyzed and following observations were obtained. Routine liver function test results were compared with laboratory reference values given in Table- 1, 2 and 3.

Inclusion Criteria: Case with acute appendicitis and its complication with test negative for HBSAg and no past history of jaundice. **Exclusion Criteria:** Case with acute appendicitis and its complication with test positive for HBSAg and /or past history of jaundice.

Results: Total number cases were 45. Of 45, 25 were males and 20 were females. Their age ranged from 11years to 60 years. The average was 27.2 years. Duration of symptoms ranged from 5 hours to maximum 9 days. Among 45 cases diagnosed as acute appendicitis clinically (preoperatively), per operatively, 36 cases had inflamed appendix, 3 cases had gangrene, 5 cases had perforation with peritonitis (4 localized and 1 generalized peritonitis) and only a single case was noted to be of normal appendix (Table 4). Liver function tests (LFT) analysis revealed following results, Among 45 cases, SB was raised in 39cases where as 6 cases had normal SB level. The raised SB ranged from 1.2 mg/dL to 8.4 mg/dL. The average level of SB was 2.38 mg/dL. All the cases had indirect fraction of SB above 15%. (Table 4). The rise in SB was without concomitant much rise in liver enzymes.

Conclusion: Following conclusion can be drawn from the present study. Firstly, There was Hyperbilirubinemia in 86.6% of the patients of acute inflammation of appendix (i.e. acute appendicitis and its complications). Secondly, Raised SB ranged from 1.2mg/dL - 8.4 mg/dL. Thirdly, The rise in SB was mixed in type (both indirect and direct). Finally, The hyperbiliubinemia was intra hepatic cholestatic in type due either to abnormality in permeability of hepatocyte or ductular membrane enzyme inhibition as the liver enzymes were not much elevated.

Key words: Acute Inflammation of Appendix, Acute appendicitis, Hyperbilirubinemia, Serum bilirubin

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Bilirubin is the end product of the metabolic degradation of haeme, prosthetic group of haemoglobin, myoglobin, the cytochrome P450s and various other hemo-proteins[1]. The serum level of bilirubin represents the balance between production and excretion (destruction) of this breakdown product. Laboratory evaluation of SB allows detection in two forms (i). Indirect or unconjugated (i.e. before hepatic metabolism (ii). Direct or conjugated (i.e. after hepatic metabolism)[2]. Since bilirubin is potentially toxic waste product, hepatic handling is designed to eliminate it from the body *via* biliary tract. There are various steps involved in this process namely; hepatocellular uptake, intracellular binding, conjugation and excretion[1]. Modern analytical methods document that normal plasma contains virtually no bilirubin conjugate. The 10-20% of the bilirubin in normal plasma that gives rise prompt (diazo) reaction is an artifact of kinetic of the van den berg reaction which with along various modifications is the method most commonly used to quantitate bilirubin in clinical laboratories. Indeed, when direct reacting fraction is less than 15% of total bilirubin at virtually any total bilirubin concentration, the bilirubin in the sample can be considered as essentially all unconjugated[1].

Conjugated bilirubin (mono- and diglucronide) is excreted across canalicular plasma membrane into the canaliculus by an ATP- dependant transport process mediated by a canalicular membrane protein called multi-drug resistant –associated protein -2. The canalicular transport mechanism of excretion of bilirubin conjugate is very sensitive to injury. Accordingly, in hepatocellular disease, as well as with either cholestasis or mechanical obstruction to the bile duct, bilirubin conjugates within the hepatocytes, prevented from taking their normal pathway into the canaliculi and down the bile duct, may reflux into blood stream, resulting in mixed or less often a truly conjugated hyperblirubinemia[1].

Hyperbilirubinemia occurs either due to cholestatic, hepatocellular or haemolytic diseases. Cholestatic and hepatocellular hyperbilirubinemia are associated with a rise in liver enzymes. In these cases the bilirubin is predominantly conjugated in type (mixed type). An isolated rise in SB (without enzyme elevation) may be familial or due to hemolysis.[3]Cholestasis is the failure of normal bile to reach duodenum. This may be due to pathology any where between the hepatocyte and ampulla of Vater. Intrahepatic cholestasis includes those conditions where there is no demonstrable obstruction to major bile duct. The causes are drugs, hormones, primary billiary cirrhosis and sepsis[3].

Sepsis reaches to the liver by various routes but one of the commonest routes is through portal vein from the gastro-intestinal tract. Any inflammatory condition may cause transmigration/ translocation of bacteria; its toxin or cytokines may cause suppression of hepatocellular function and reduced excretion of bile from billiary canaliculi[4]. One of the commonest abdominal organ that goes into inflammation is appendix. It comprises 55% of total cases of acute abdomen[5]. It is also a primary cause of right lower quadrant acute abdominal pain in and around Kathmandu valley[5]. Due to this Dieulfoy (1898) coined the term *le foie appendiculaire* for appendicitis and recommended early surgical treatment[6].

Various studies have shown that portal pyaemia may follow pelvic or gastro intestinal infection resulting in portal phlebitis or septic emboli. It can follow appendicitis, empyema gall bladder, diverticulitis, regional enteritis[7, 8] perforated gastric and colonic ulcers, leaking anastomosis, and pancreatitis[9]. Appendicitis was the most common source of portal pyaemia in earlier series reporting 35% of total group of Oschner's patients. [10] Appendicitis is now involved in no more than 10% of cases in more recent series[11]. It is widely accepted that the inciting event in most instances of appendicitis is obstruction of lumen (partial/complete) causes accumulation of secretion and distention of lumen, which rises intra- luminal pressure. This leads to first lymphatic later venous obstruction and bacterial over growth and oedema. An inflammatory response causes the appendix to become more oedematous and ischemic. Subsequently, transmigration of bacteria through the ischemic wall happens[4].

The mechanism of hepatic injury in sepsis is not completely understood. This could be because of bacteria, its toxin or cytokines. In early sepsis with hyper-dynamic circulation bacteria, its toxin or cytokines are involved where as in late sepsis; ischemia due to decreased hepatic blood flow to the liver is the mechanism of hepatic injury. In both above situations the hepatic injury leads to dysfunction of hepatocyte and tubule leading to mixed type of hyperbilirubinemia (hepatocellular and intra hepatic cholestasis)[12]. Cholestasis in severe bacterial infection, particularly in childhood or post operatively, is presumably hepatocellular in nature. It can also be related to cholestatic effect of endotoxin on sodium-potassium-ATPase[3]. All the constituents of bile show an increased level in serum. Conjugation of billiary substance is intact but excretion is defective. Serum alkaline phosphatase is raised. The rise is due to increase synthesis or release of enzymes

from liver or biliary plasma membrane[3]. The minimal hepatocellular damage may be suspected by noting minimal elevated transaminase value and some times SB.

Material and methods

This is a prospective study conducted at NGMC Teaching hospital Nepalgunj Nepal during October 2004- October 2005. 45 Consecutive cases of acute appendicitis admitted in surgical unit III were recruited for the study. Clinically suspected cases were subjected to investigations to confirm the diagnosis. Investigations included total leucocytes count, differential leucocytes count, urine analysis and ultrasound. These cases were also subjected to liver function test. Subsequently these cases were operated and clinical diagnosis was confirmed per–operatively and post operatively by histo-pathological examination of specimen. Their clinical and investigative data were compiled and analyzed, and following observations were obtained. Routine liver function test results were compared with laboratory reference values given in Table- 1, 2 and 3.

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Table 1: Reference Range of SB and Liver Enzymes*

Test	Normal Range
Serum Bilirubin	
Total	1.1mg/dL
Direct	0.2mg/dL
Liver Enzymes	
SGPT	≤ 35U/L
SGOT	≤ 40U/L

*Semi-automatic analyzer measured SB and enzymatic assay measured liver enzymes

Table 2: Reference Range of Alkaline Phosphatase (ALP) in Children*

Age Group	Normal Range	
	Female (U/L)	Male (U/L)
1-30 days	48-406	75-319
1 month – 1 year	124-341	82-383
1-3 years	108-317	104-345
4-6 years	96-297	93-309
7-9 years	69-325	86-315
10-12 years	51-332	42-362
13-15 years	50-162	74-390
16-18 years	47-119	52-171

*Soldin JS , Hicks JM. Paediatric reference ranges. Washington: AACC Press, 1996. p. 5.

Table 3: Reference Range Of ALP in Adult Population*

Age Group	Normal Range	
	Male (U/L)	Female (U/L)
20-50	53-128	42-98
> 50	56-119	53-141

*Burtis CA, Ashwood ER. Eds. Teitz textbook of clinical chemistry. 3rd ed.Philadelphia: W.B. Saunders Company, 199, p. 1829

Results

Table 4 show characteristics, clinical presentation and results of liver function test. Total number cases were 45. Of 45, 25 were males and 20 were females. Their age ranged from 11years to 60 years. The average was 27.2 years. Duration of symptoms ranged from 5 hours to maximum 9 days. Among 45 cases diagnosed as acute appendicitis clinically (preoperatively), per operatively, 36 cases had inflamed appendix, 3 cases had gangrene, 5 cases had perforation with peritonitis (4 localized and 1 generalized peritonitis) and only a single patient had normal appendix. LFT revealed following results, Among 45 cases, SB was raised in 39 (86.6%) cases where as 4 (13.4%) cases had normal SB level (Fig. 2). It ranged from 1.2 mg/dL to 8.4 mg/dL. The average level of SB was 2.38 mg/dL. All the cases had indirect fraction of SB above 15%.

Liver enzymes e.g. Alanine aminotransferase (ALT, SGPT) was within normal ranges in 34 (75.5%) cases where as 11 (24.5%) cases had elevated enzyme level (Fig.3). Cases who had raised ALT level, 8 (17.7%) cases had values below 52 U/L (<11/2 times of normal value) where as 3 (6.66%) cases had values below 102U/L (<3 times of normal value). The raised level ranged from 37-102 units/litre with an average of 59.1 units/litre.

Aspartate aminotransferase (AST, SGOT) was with in normal limits in 29 (64.4%) cases whereas 16(35.6%) cases had elevated levels. The elevated AST ranged from 41-83 unit/litre with an average 54.8-units/ litre. The rise in all cases was less than <3 times (<100U/L) of the normal range.

Similarly, age adjusted alkaline phosphatase (ALP) was raised in 22 (48.8%) cases where as 23 (51.2%) cases had no rise in enzyme level. The rise in all the cases was also less <3 times of the normal values to the respective age and sex (within normal limits in 51.11%, Moderate to minimal elevation (1-2 times) in 48.8% of patients).

Table 4: Characteristics, clinical presentation, Liver function test

CASES					LIVER FUNCTION TEST					
S. N.	Sex	Age	Duration of symptoms	Diagnosis	Serum Bilirubin			Liver Enzymes		
				Clinical / Operative	Total	Direct	Indirect	SGPT	SGOT	ALP
					mg/dL	mg/dL (%)	Mg/dL (%)	U/L	U/L	U/L
1	F	17	9 d*	AA / AP	8.4	2.2 (26.1%)	6.2 (73.9%)	18	40	80
2	F	50	4 d	AA / AG	4.3	2.0 (46.5%)	2.3 (53.5%)	25	25	102
3	M	32	2 d	AA / AA	2.0	0.7 (35.0%)	1.3 (65.0%)	23	17	131
4	M	21	1 d	AA / AA	1.0	0.2 (20.0%)	0.8 (80.0%)	24	55	272
5	M	40	1 d	AA / AA	3.7	1.3 (35.1%)	2.4 (64.9%)	102	60	104
6	M	50	1 d	AA / AA	1.5	0.5 (33.0%)	1.0 (66.7%)	90	33	376
7	M	32	2 d	AA / AG	3.1	2.1 (67.7%)	1.0 (32.3%)	52	72	162
8	F	28	1 d	AA / AA	3.1	0.9 (29.0%)	2.2 (71.0%)	23	25	165
9	F	60	3 d	AA / AA	1.5	0.4 (26.6%)	1.1 (73.4%)	23	58	104
10	M	31	1 d	AA / AA	0.9	0.3 (33.3%)	0.6 (66.7%)	18	41	50
11	M	31	2 d	AA / AP	2.0	1.2 (60.0%)	0.8 (40.0%)	20	26	100
12	F	55	3 d	AA / AP	5.9	4.0 (67.7%)	1.9 (32.3%)	33	45	254
13	M	15	3 d	AA / AP	3.1	0.7 (22.5%)	2.4 (77.5%)	22	44	584
14	M	38	3 d	AA / AA	2.0	1.2 (60.0%)	0.8 (40.0%)	20	26	108
15	F	15	2 d	AA / AP	3.0	2.0 (66.0%)	1.0 (34.0%)	16	37	373
16	M	13	1 d	AA / AA	3.0	0.7 (23.3%)	2.3 (76.7 %)	30	36	52
17	M	31	1 d	AA / AA	1.9	0.3 (15.7%)	1.6 (84.3%)	18	41	88
18	M	32	1 d	AA / AA	1.6	0.4 (25.0%)	1.2 (75.0%)	22	44	70
19	F	31	5 d	AA / AA	1.2	0.2 (16.6%)	1.0 (83.33%)	10	18	130
20	F	26	5 h**	AA / AA	1.7	0.4 (23.5%)	1.3 (76.5%)	14	19	118
21	F	22	3 d	AA / AA	4.0	2.1 (52.5%)	1.9 (47.5%)	16	36	140
22	M	23	3 d	AA / AA	1.4	0.6 (42.8%)	0.8 (57.2%)	68	76	61
23	F	11	4 d	AA / AA	1.2	0.6 (50.0%)	0.6 (50.0%)	06	16	50
24	M	15	2 d	AA / AA	2.0	0.1 (50.0%)	1.0 (50.0%)	17	24	153
25	F	20	3 d	AA / AA	1.1	0.2 (18.1%)	0.9 (81.9%)	18	14	221
26	M	10	3 d	AA / AA	2.0	0.5 (25.0%)	1.5 (75.0%)	18	27	220
27	F	15	3 d	AA / AA	2.0	0.1 (50.0%)	1.0 (50.0%)	12	24	153
28	F	22	1 d	AA / AG	4.0	2.1 (52.5%)	1.9 (47.5%)	16	36	140
29	M	40	1 d	AA / AA	1.5	0.7 (50.0%)	0.7 (50.0%)	46	76	84
30	M	30	2 d	AA / AA	3.0	0.8 (26.6%)	2.2 (73.4%)	37	27	48
31	M	40	2 d	AA / AA	5.0	3.0 (60.0%)	2.0 (40.0%)	29	71	170
32	F	15	1 d	AA / AA	2.0	1.0 (50.0%)	1.0 (50.0%)	12	24	153
33	M	13	2 d	AA / AA	2.0	1.0 (50.0%)	1.0 (50.0%)	10	83	847
34	F	21	1 d	AA / AA	0.9	0.2 (22.2%)	0.7 (77.8%)	38	24	161
35	F	36	1 d	AA / AA	1.2	0.4 (33.3%)	0.8 (66.7%)	14	25	242
36	F	31	5 d	AA / AA	1.2	0.2 (16.66%)	1.0 (83.34%)	10	18	130
37	F	26	5 h	AA / AA	1.7	0.4 (23.52%)	1.3 (76.48%)	14	19	118
38	M	22	3 d	AA / AA	4.0	2.1 (55.5%)	1.9 (44.5%)	16	36	140
39	M	20	2 d	AA / AA	2.0	1.0 (50.0%)	1.0 (50.0%)	44	17	117
40	M	28	2 d	AA / AA	3.0	0.9 (30.0%)	2.1 (70.0%)	33	38	83
41	F	15	1 d	AA / N	1.0	0.3 (30.0%)	0.7 (70.0%)	22	21	60
42	M	25	1 d	AA / AA	0.7	0.4 (57.14%)	0.3 (42.86%)	45	42	245
43	M	22	1d	AA/AA	2.0	0.8(40.0%)	1.2(60.0%)	17	58	175
44	F	30	3d	AA/AA	1.4	0.5(35.7%)	0.9(64.3%)	52	45	83
45	M	20	2d	AA/AA	2.0	1.0(50.0%)	1.0(50.0%)	44	17	117

AA=Acute Appendicitis, AG=Appendicular Gangrene, AP=Appendicular Perforation
d* = Days, h** = Hours

Fig. 1 Peroperative Diagnosis

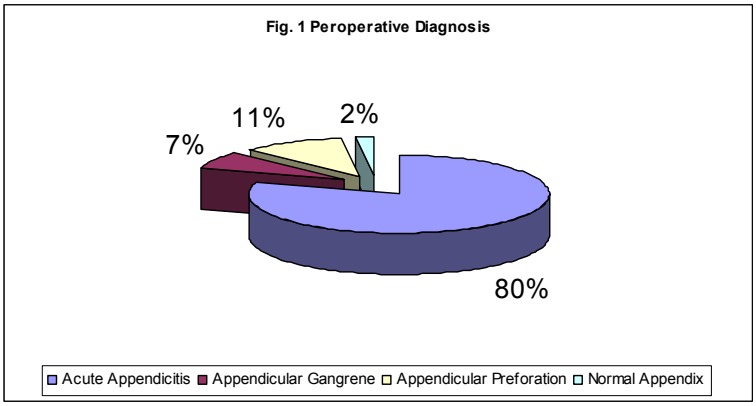

Fig. 2 Distribution of Serum Bilirubin

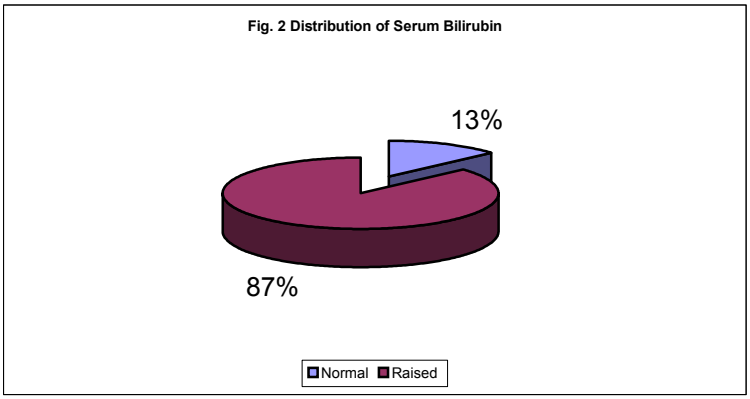

Fig. 3 Distribution Of SGPT (ALT)

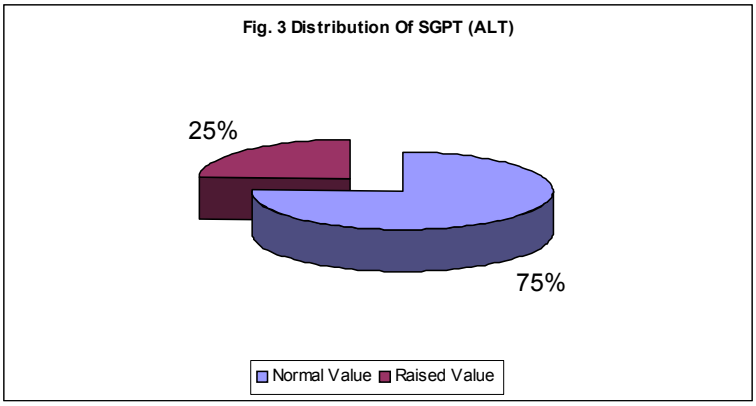

Table 5: Age Group Wise Distribution of the Cases

Age Group	No. of cases (%)
(0-10	Nil
10-20	11 (24.4)
20-30	15 (33.3)
30-40	12 (26.7)
40-50	03 (06.7)
50-60	04 (08.9)
>60	Nil
Total	**45 (100)**

Table 6: Distribution of SB

Serum Bilirubin Level	No. Of cases (%)
Raised serum bilirubin (Hyperbilirubinemia)	39 (86.6)
Normal	06(13.4)
Total	**45(100)**

Table 7: Duration of symptoms

In Hours	No. Of cases (%)
< 24	02(04.4)
24 – 48	16(35.6)
48 – 72	22(48.9)
>72	05(11.1)
Total	**45 (100)**

Discussion

Hyperbilirubinemia may be due to haemolysis, hepatocellular damage or cholestasis (intra and extra hepatic out flow obstruction). The biochemical picture of elevated SB in haemolysis is unconjugated (indirect) type where as mixed type in hepatocellular and cholestasis diseases (conjugated and unconjugated).[1]

In the present study, the over all picture of LFT suggests elevation in conjugated and unconjugated SB (mixed type of hyperbilirubinemia) in most of the patients (86.6%). But at the same time, there was no elevation or minimal elevation (<100U/L) in ALT and AST in most of the cases (99.0% and 100.0% respectively). Similarly, ALP was either with in normal limit or minimal to moderate elevation in all cases (100.0%).

The above observations suggest that there is no damage but dysfunction of hepatocytes. The dysfunction is either derangement in permeability of hepatocytes to bilirubin or depressed function of ductule enzyme (Na-K ATP ase) leading to cholestasis, regurgitation and mixed type of hyperbilirubinemia.

The present results are similar to the experimental study of Whiting et. al., in which they have demonstrated depressed excretion of bile in canaliculi.[13] This finding is further supported by demonstrating inspissated bile in dilated proliferated and peri-portal ductules in the histopathological study of liver.[14]

The hepatocellular dysfunction/damage in sepsis may be either due to bacteria, its toxin or cytokines. The agent reaches from inflamed gut via portal vein or lymphatic with the process of transmigration or translocation. Bacterial translocation is the process by which bacteria moves across the mucosal barrier and invades the host. This phenomenon can occur in small percentage of healthy persons. The process seems to be accelerated with starvation and injury.

This has been proved by demonstrating bacteria in portal blood in 30% with non-inflammatory bowel disease.[15] But these patients do not develop any disease because of hepatic clearance of portal bacteria is very efficient and It is very common event in healthy persons. So, human liver remains sterile in most of the circumstances. To develop liver disease, adequate amount of bacteria and vulnerable liver is needed. Bacterial involvement in dysfunction or damage has been proved by various direct, indirect, clinical and experimental studies.

Indirect evidences of bacterial translocation from inflamed gastro intestinal tract or peritonitis to liver via portal vein and development of hepatitis, pyogenic liver abscess was observed by Fitz[16] and Dieulfoy[6] in their clinical studies. They have demonstrated two classical findings. Firstly; simultaneous inflammation of the intestine (e.g. appendix), peritoneum and development of pyogenic liver abscesses, Secondly; bacteriological similarities of the gastrointestinal tract and pyogenic liver abscesses. These bacteria commonly reaches to liver from intra- abdominal organs, commonly from the commonest organ involved in inflammation that was appendix. So he coined the term *le foie appendiculaire* in describing multiple hepatic abscesses subsequent to perforated appendicitis with pyelephlebitis. Similarly, Oshner and Debakey[9]also provided classical treatises on pyogenic infection. These authors revived personal experiences and world literature, and emphasized its pathogenesis and clinical presentation. Bacteria isolated in pyogenic liver abscesses were similar to the bacteria involved in acute inflammation of the gut (i.e. acute appendicitis) and peritonitis. These agents were E. coli, Streptococcus fecalis, Klebsiella and Proteus vulgaris. Commonly the infection were of mixed type.[9,17,18] So, it was concluded from indirect evidences that pyogenic liver abscesses developed from the bacteria actually transmigrated from inflamed gut.

Direct evidences, of bacterial translocation from inflamed organ was observed in clinical and experimental studies. Recently in one study blood samples from superior mesenteric vein in acute appendicitis showed bacteria in 38% of patients.[19] similarly; it has also been observed in experimental study done on Gonobiotic mouse model, that showed micro-organism moving from gut into lymphatics.[20] These finding suggest that bacteria may transmigrate and produce portal bacteraemia, hepatocellular dysfunction or pyogenic liver abscess. The hepatocellular dysfunction in majority of the cases cannot be explained only with the 38%of positive culture of bacteria from superior mesenteric blood. So there may be role of some other substances in the development of the disease.

The role of other substances have been demonstrated very recently, in five experimentally studies on rats. It has been shown that liver dysfunction is caused by cytokines released from gut due to injury /inflammation. In this study rats were subjected to intra-abdominal sepsis from caecal ligation and puncture and following observations were made (i). Small intestine is important source of adrenomedullin release during poly microbial sepsis[21] (ii). Nor-epinephrine induced hepatocellular dysfunction in early sepsis, mediated by activation of alpha-2 adreno-receptor[22] (iii). TNF produces hepatocellular dysfunction despite of normal cardiac out put and hepatic microcirculation[23] (iv). Hepatic extraction of indo-cyanine green is depressed early in sepsis despite of increased hepatic blood flow and increase in cardiac out put.[23]

So, it is concluded that hepatocellular function is depressed during early stage of sepsis despite the increased cardiac output and hepatic blood flow and decrease peripheral resistance. The depression of hepatocellular function in 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 inter- leukin-6. This observation is further duplicated by administration of recombinant murine TNF –alpha at a dose that does not reduces cardiac output and hepatic perfusion produces hepatocellular dysfunction and increases IL-6.[24] Thus up regulation of TNF and/ or IL-6 may be responsible for producing hepatocellular dysfunction during early hyper-dynamic stage of sepsis.[13]

Conclusion

Following conclusion can be drawn from the present study. Firstly, there was Hyperbilirubinemia in 86.6% of the patients of acute inflammation of appendix (i.e. acute appendicitis and its complications). Secondly; Raised SB ranged from 1.2mg/dL - 8.4 mg/dL. Thirdly, the rise in SB was mixed type. Finally, the hyperbilirubinemia is because of hepatocellular cholestasis, may be either derangement in permeability of hepatocytes to bilirubin or depressed function of ductule enzyme (Na-K ATP ase) leading to cholestasis, reflux and mixed type of hyperbilirubinemia

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