ORIGINAL RESEARCH PAPER
Volume-6 | Issue-12 | December-2017 | ISSN No 2277 - 8179 | IF : 4.176 | IC Value : 93.98
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

BILE INFECTION AND ITS IMPACT ON LIVER IN PATIENTS OF GALL STONE DISEASE

Surgery

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ABSTRACT

Context: Diseases of gallbladder are very common in digestive tract disorders the commonest being cholelithiasis. Gallstone disease not only affects the biliary tree but can also cause bile infection and biliary microorganism is known to cause significant liver injury.
Aims: To see the bile infection and its impact on liver in patients of GSD (Cholelithiasis, Chronic cholecystitis, CBD Stones)
Material and Methods: All patients being subjected for planned cholecystectomy were taken as subjects irrespective of age, sex and co-morbid conditions.
Results: 90 patients were included in study. In 78 out of 90 patients bile culture was sterile and in 12 patients it was infected. Choledocholithiasis was associated with a greater incidence of positive bile culture and abnormal liver histology.
Conclusions: Infected bile leads to more damage to liver and incidence of infected bile and liver histology changes is more in choledocholithiasis.

KEYWORDS

Cholelithiasis, choledocholithiasis, liver histology, bile infection

INTRODUCTION

Gall bladder is a pear shaped organ adherent to the under surface of liver[1]. The primary purpose of gallbladder is to store and concentrate bile, a greenish brown fluid that is produced by the liver. Bile is needed to digest and absorb fatty food and to absorb important fat soluble vitamins.

Diseases of gallbladder are very common in digestive tract disorders the commonest being cholelithiasis (derived from Greek word chole meaning bile, lith meaning stone and iasis meaning process). In the present time cholecystectomy remains the standard treatment of cholelithiasis despite the advent of gallstone dissolving drugs and extracorporeal lithotripsy. This disorder, which constitutes a major burden on the community (prevalence 6%)[2], is more common in females as compared to males (3:1) and in approx 15% cases first degree relatives are affected[3].

Gallstone disease not only affects the biliary tree but can also cause bile infection and these two combined can lead to significant hepatic parenchyma damage. Biliary microorganism is known to cause significant liver injury. Rate of positive bile culture are significantly high in patients of acute cholangitis (84%) and choledocholithiasis (58.2%) as compared to cholelithiasis (3%).

Early intervention in these cases not only retards the unwanted effects but also prevents irreversible damage to liver. This present study has been undertaken with a view to elicit information on bile infection consequent to gallstone disease and its effect on liver in Indian patients.

AIMS AND OBJECTIVES

To see the bile infection and its impact on liver in patients of GSD (Cholelithiasis, Chronic cholecystitis, CBD Stones)

MATERIALS AND METHODS

Study Setting – This study was conducted in the Department of Surgery for one year at a tertiary care teaching hospital in Delhi. Prior clearance by the college ethical committee was obtained.

Sample Size – 90.

Inclusion Criteria - All patients being subjected for planned cholecystectomy were taken as subjects irrespective of age, sex and co-morbid conditions. Patients of CBD stones were also included, after following the existing protocol for CBD stone i.e., ERCP (endoscopic retrograde cholangiopancreatography) guided stone removal followed by routine cholecystectomy

Exclusion Criteria

1. Recent history of medical Jaundice(<3 months)
2. Patients on hepatotoxic drugs.
3. Patients of Portal hypertension
4. Patients with Hepatitis B or Hepatitis C.
5. Deranged coagulation profile.
6. Patients with acute cholecystitis.
7. Patients with fatty liver on USG.
8. Patient not willing/giving consent.

Informed Consent – Informed consent was taken during the workup in OPD, patients and relatives were told about the nature of study and procedure.

All patients underwent a detailed physical examination with special reference to the hepatobiliary system.

Lab Investigations

a) Haemoglobin
b) Total and differential leukocyte counts
c) Kidney function tests
d) Liver Function tests
e) Prothrombin time and INR

Radiology – Ultrasound was the primary diagnostic modality in all patients.

Type Of Surgery – All the patients undergoing laparoscopic or open cholecystectomy were included in this study.

Technique of Bile Aspiration- Bile was aspirated from GB after proper identification of structures in both open and laparoscopic technique.

Technique of Liver Biopsy- In both open and laparoscopic technique after gall bladder aspiration cholecystectomy was done. After gall bladder was taken out hemostasis was achieved around gall bladder fossa. Undamaged portion of the liver edge was selected and held by atraumatic forceps, using a sharp scissors around 1 cm of liver edge was taken out and sent for histopathological examination. Haemostasis was secured using electrocautery.

Specimens Sent-

1) Bile aspirate for culture and sensitivity.
2) Gall bladder for histopathological examination.
3) Liver edge for histopathological examination

STATISTICAL ANALYSIS

Normally distributed continuous variables were compared using the unpaired t test, whereas the Mann-Whitney U test was used for those variables that were not normally distributed. Categorical variables were analysed using either the chi square test or Fisher's exact test. P<0.05 was considered statistically significant.

OBSERVATIONS AND RESULTS

Total of 90 patients were included in the study, minimum age was 18 years, maximum age was 64, mean age was 38 and most frequent age group was 40 – 49 years (33%).

Out of 90 patients 78(86.7%) were females and 12 were males.

All the patients were symptomatic; the patients with acute cholecystitis were excluded from the study. The duration of symptoms in months were asked and noted. The maximum duration was 48 months, minimum was 4 months and mean duration was 17 months.

Out of 90 patients 8 patients had given history of jaundice. Only patients who had jaundice due to gall stones were included in the study and patients who had medical jaundice were excluded from the study.
28 out of total 90 patients had some form of co-morbid conditions like diabetes mellitus, hypertension and thyroid diseases.

None of the patients had signs of acute inflammation at the time of admission for surgery; liver and gall bladder were not palpable in any of the patients.

3 out of 90 patients had icterus and all 3 had history of choledocholithiasis for which 2 of the patients underwent ERCP and CBD stone removal, one patient underwent CBD exploration at the time of cholecystectomy.

Liver function test including bilirubin, SGOT, SGPT, alkaline phosphatase was done in all the patients. It was within normal range in all the patients except 5 patients of choledocholithiasis.

All the 90 patients had evidence of chronic cholecystitis on USG. All the patients had stones in gall bladder. 11 out of 90 patients had single stone in gall bladder lumen, 79 patients had multiple stones in gall bladder.

Nature of Gall Bladder Aspirate- As soon as gall bladder was identified during surgery it was punctured by an aspiration needle and GB aspirated. Naked eye examination of the aspirate was done and the observation noted in patient proforma. In 80 patients the aspirate was bile, in 8 patients it was clear mucus like fluid and in 2 patients it was purulent.

Bile Culture- After gall bladder aspiration in all patients the aspirate i.e. bile, mucus or pus was sent for aerobic culture. In 78 out of 90 patients bile culture was sterile and in 12 patients it was infected.

Type Of Organism In Infected Bile- Out of 12 samples in which bile was infected Escherichia coli was found in 7 samples, Klebsiella was found in 3 samples and Enterococcus was found in 2 Samples.

Liver Histology- Liver biopsy was examined by light microscopy in all 90 patients. In 54 patients liver biopsy was absolutely normal but in 36 patients significant changes were present in liver histology.

Gall Bladder Histology- In all 90 patients chronic cholecystitis was present; in some cases along with chronic cholecystitis cholesterosis was also present.

Gall Bladder Aspirate and Liver Histology

Out of total 90 patients on aspiration of gall bladder in 80 patients it was bile, in 08 patients it was mucus and in 02 patients it was pus. This gall bladder aspirate was compared with liver histology. The 'p' value came out to be 0.791 which is not significant. (Table 1)

GB ASPIRATE	Liver Histology Present		Liver Histology Absent		P value
	Frequency	%	Frequency	%	
Bile (80)	31	86.1%	49	90.7%	0.791
Mucus (08)	4	11.1%	4	7.4%	
Pus (02)	1	2.8%	1	1.9%	
Total	36	100%	54	100%	

Table 1- Gall Bladder Aspirate and Liver Histology
Choledocholithiasis and Bile Culture 3 out of 5 patients of CBD stones had infected bile. 3 infected samples had E.Coli, Klebsiella and enterococcus each.

The percentage of E.Coli, Klebsiella and enterococcus is 20% each in patients of common bile duct stone whereas in patients not having CBD stone the percentage was 7.1% for E.Coli, 2.4% for Klebsiella and 1.2% for Enterococcus. 'P' value for this was 0.003 which is stastistically significant. (Table 2)

BILE CULTURE	No CBD Stone		CBD Stone		P value
	Frequency	%	Frequency	%	
E.coli (07)	6	7.1%	1	20.0%	0.003
Enterococus (02)	1	1.2%	1	20.0%	
Klebsiella (03)	2	2.4%	1	20.0%	
Sterile (78)	76	89.4%	2	40.0%	
Total	85	100%	5	100%	

Table 2- Bile culture and Choledocholithiasis Biliary Bacteriology and Liver Histology

The study group was subdivided into those with infected bile and those without, they were then analysed for the incidence of various histological changes. The 'p' value in case of portal tract infiltration with bile culture was 0.003 which is statistically significant. In other histological parameters apart from portal tract infiltration like fatty change, cholestasis, lobular parenchymal infiltration and fibrosis it is not significant. The findings are tabulated below. (Table 3 & 4)

BILE CULTURE	Liver Histology Present		Liver Histology Absent		P value
	Frequency	%	Frequency	%	
E.coli	5	13.9%	2	3.7%	0.052
Enterococus	2	5.6%	0	0.0%	
Klebsiella	2	5.6%	1	1.9%	
Sterile	27	75.0%	51	94.4%	
Total	36	100%	54	100%	

Table 3- Bile culture and Liver Histology

Liver Histology	Bile Culture				P value
	Positive (n=12)	%	Negative (n=78)	%	
Fatty Change	3	25.0%	13	16.7%	0.441
Cholestasis	3	25.0%	6	7.7%	0.096
Lobular Parenchymal Infiltration	2	16.7%	4	5.1%	0.181
Portal Tract Infiltration	7	58.3%	15	19.2%	0.003
Fibrosis	0	0.0%	1	1.3%	1.000

Table 4- Liver Histological changes and relation with Bile Culture

DISCUSSION

Gall Bladder Stone and Aspirate Vis-A-Vis Liver Histology

In the present study, out of 90 patients 79 had multiple gall stones and 11 patients had single stone. This observation was noted on ultrasonography and confirmed after gall bladders were taken out during surgery. Out of 79 patients having multiple gall stones in 31 patients liver histopathology changes were present and in 48 patients liver biopsy was normal. Out of 11 single stone patients in 5 patients there were changes in liver biopsy and in 6 patients it was normal. The 'p' value was 0.69 which is statistically insignificant. Hence it can be said that number of stones does not affect the changes in liver histopathology in patients of gall stone disease. In none of the studies done previously correlation of number of stones and liver histology has been seen.

In the current study gall bladder was aspirated and the aspirate sent for culture at the start of surgery. Out of 90 patients it was bile in 80, mucus in 8 and pus in 2 patients. Out of 80 patients having bile in the aspirate, liver histology was significantly changed in 31 patients and in 49 patients it was normal. 4 patients having mucus as gall bladder aspirate had changes in liver biopsy and in 4 such patients it was normal. One patient having pus aspirate demonstrated liver histology change and one did not. The 'p' value was 0.791 which is statistically insignificant.

Hence liver histopathology does not depend upon the nature of gall bladder aspirate in gall stone disease. In similar studies done previously this variable was not used.

Biliary Bacteriology and Histopathology Of Liver

It is believed that cholecystitis has a higher incidence of septic complications and the incidence increases further if the common bile duct is explored (Keighley[4] 1977, Wolloch[5] 1977). Csendes et al[6] (1975) and Nielsen et al[7] (1976) have suggested that bile is usually sterile unless biliary tree is diseased.

In the present study biliary culture for aerobic bacteria was done in all patients. The bile was sterile in 78 (86.7%) patients and infected in 12(13.3%) patients. Escherichia coli was present in 7(7.8%) patients, Klebsiella in 3(3.3%) and Enterococcus in 2(2.2%) patients. On applying Chi square test in biliary bacteriology and liver histology, 'p' value is significant (0.003) for portal tract inflammation; for rest of the liver the correlation of histology changes with biliary bacteriology was not significant.

Various studies had done previously shows different results. Chetlin and Elliot[8] reported on 240 patients and observed positive bile culture in 17% of chronic cholecystitis patients, 60% of acute cholecystitis and 58% of common bile duct stone patients. Flinn[9] (1977) found positive bile culture in 23(34%) of patients. All 6 patients of common bile duct stone had positive bile culture, E.Coli was most common organism followed by klebsiella and enterococcus.

Maluenda F[10] (1989) found in patients of acute suppurative cholangitis and choledocholithiasis a higher percentage of E.Coli and klebsiella. JM Geraghty[11] (1994) found positive bile culture in 10 out of 42 patients. In this study also the most common organism was Escherichia coli.

George RK[12] (2002) had found positive bile culture in 7 out of 50 patients and they said that biliary infection was associated with significant incidence of fatty change and inflammatory cell infiltrate. Chang WT[13] (2002) found 25% positive bile culture for gall bladder stone and 66% for common bile duct stone. Most common being again Escherichia coli (36%). Shivaprakasha S[14] (2006) also found E.Coli (30%) as the most common organism followed by klebsiella and enterococcus in biliary tract disease. Bae WK[15] (2008) study also gave similar results.

The findings from our study reveal that positive bile culture is significantly associated with portal tract infiltration. However, other histological findings are also common in patients with biliary infection but they are statistically not significant.

Choledocholithiasis and Liver Histology and Bile Culture

Liver damage in patients with gall stones has been considered to be secondary to chronic extrahepatic large bile duct obstruction. This obstruction may or may not be accompanied by repeated episodes of cholangitis and may ultimately progress to secondary biliary cirrhosis (Scobie et al[16] 1965). Failure to relieve mechanical obstruction to bile flow may lead to secondary biliary cirrhosis, the degree of mechanical obstruction present and the frequency and severity of cholangitis which may develop may determine the course of disease progression. In adults it has been estimated that secondary biliary cirrhosis develops 4.5 years after the onset of mechanical obstruction due to a calculous (Scheur PJ[17] 1984).

In the present study 5 patients had choledocholithiasis, 4 patients underwent endoscopic retrograde cholangiopancreatography and stone removal from common bile duct before they were taken up for cholecystectomy and one patient underwent CBD exploration at the same sitting with cholecystectomy. Significant liver histology changes were present in 4(80%) patients and all the 4 patients had portal tract infiltration and cholestasis. Bile culture was infected in 3(60%) patients and 'p' value for this was 0.003 which is statistically significant.

Similar studies on liver histology in choledocholithiasis showed a higher incidence of significant changes in patients of common bile duct stone. WR Flinn[9] (1977) study showed 7 out 12 patients of choledocholithiasis had significant liver histology changes. Intrahepatic cholangitis was found mainly in patients of CBD stone (Badke[18] 1983). In study of Geraghty[11] (1994) 11 out 14 patients had significant liver changes.

There is high incidence of infected bile in patients of common bile duct stone which is proved in the present study and the fact is supported by previous studies. Infected bile was found in 66% of CBD stone in the study by Chang WT[13] 2002, in 100% in the study by Flinn[9] 1977 and in 43% in the study by Geraghty[11] 1994. Chetlin and Scott[8] found 58% and 83% infected bile respectively in patients of common bile duct stone.

CONCLUSION

Gall stone disease cause significant changes in liver histology and these changes are more common in those patients having long duration of symptoms. Infected bile leads to more damage to liver as compared to non-infected bile. In patients of choledocholithiasis incidence of infected bile and liver histology changes are more as compared to cholelithiasis with chronic cholecystitis.

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