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Treatment of Choledocholithiasis in Patients with Liver Cirrhosis

Surgical Treatment or Endoscopic Sphincterotomy?

Masanori Sugiyama, M.D., Yutaka Atomi, M.D., Akira Kuroda, M.D., and Tetsuichiro Muto, M.D.

From the First Department of Surgery, Tokyo University School of Medicine, Tokyo, Japan

Objective
The clinical features of choledocholithiasis were analyzed in cirrhotic patients. The outcomes of surgical treatment and endoscopic sphincterotomy (EST) in this situation were compared and the risk factors predictive of an increased mortality rate were identified.

Summary Background Data
In cirrhotic patients, high risk for gallbladder stones in cholecystectomy has been established. Common bile duct stones can often exacerbate liver dysfunction and might be more difficult to treat.

Methods
Among 16 cirrhotic patients with choledocholithiasis, 9 underwent choledocholithotomy and T-tube placement (surgery group) and 7 underwent EST (EST group). Pretreatment clinical data were comparable between groups.

Results
Among 16 patients, 15 had biliary tract symptoms and 7 had cholangitis. The surgery group had excessive intraoperative hemorrhage (1576 mL) and a high morbidity rate (66.7%). The mortality rate was 44.4%: 0% in Child A or B classification patients and 80% in Child C patients. The common causes of death were liver failure, postoperative hemorrhage, and sepsis. The EST group had no complications related to procedures, but there was one death (14.3%) due to preexisting liver failure. Hepatic dysfunction, coagulopathy, and cholangitis were factors predictive of an increased mortality rate.

Conclusions
Choledocholithiasis in cirrhotic patients should be treated by EST after liver function and general condition are improved by medical management, except in emergency cases.

Cholelithiasis often accompanies liver cirrhosis.[1,2] In cirrhotic patients, gallstones are predominantly located in the gallbladder with few symptoms and complications.[3,4] However, cholecystectomy in cirrhotic patients has intraoperative and postoperative massive bleeding and high morbidity and mortality rates.[5,6] Common bile duct stones are sometimes found in patients with liver cirrhosis. These stones can often exacerbate liver dysfunction to the state of hepatic failure as a result of biliary obstruction or cholangitis. In cirrhotic patients, the

treatment of common duct stones might be more difficult than that of gallbladder stones.

In this study, the clinical features of choledocholithiasis in patients with liver cirrhosis were compared with those of cholecystolithiasis. Furthermore, we evaluated the outcomes of surgical treatment and endoscopic sphincterotomy (EST) for common duct stones in cirrhotic patients and identified risk factors predictive of an increased mortality rate.

PATIENTS AND METHODS

Between 1972 and 1991, 16 patients with liver cirrhosis were treated for choledocholithiasis at the First Department of Surgery, Tokyo University School of Medicine, Tokyo, Japan. None of these patients had simultaneous operations for diseases other than cholelithiasis. Of these 16 patients, 10 were men and 6 were women. The mean age was 63.3 years (range, 29 to 91 years).

Liver cirrhosis was diagnosed by inspection and liver biopsy at laparotomy in the nine surgical cases. For the seven patients treated by EST, the diagnosis was based on percutaneous liver biopsy in four, autopsy in one, or clinical signs, blood liver chemistry tests, and imaging studies in two. Liver cirrhosis was linked to alcohol abuse in six patients, non-A non-B hepatitis in six (anti-hepatitis C virus was not tested; post-transfusion hepatitis in three of the six), and B-type hepatitis in four. Patients with primary or secondary biliary cirrhosis were not included.

The gallstones were located in the common bile duct alone in ten patients (one of the ten had undergone cholecystectomy 22 years ago) and in both the gallbladder and common duct in six.

Of these 16 patients, 9 had surgery (surgery group): cholecystectomy, choledocholithotomy, and T-tube placement in 7 and choledocholithotomy and T-tube placement in 2. The remaining seven underwent EST (EST group). One of the seven had untreated gallbladder stones. Common bile duct stones were extracted by basket forceps immediately after EST. Two of the seven had endoscopic naso-biliary drainage (ENBD)[7] after these procedures. We treated cirrhotic patients with choledocholithiasis surgically before 1985 and with EST after 1986. Except in urgent cases, surgery or EST was performed after an attempt was made to improve the patient's condition with intense medical management consisting of intravenous hyperalimentation and the administration of fresh frozen plasma, vitamin K, diuretics, and antibiotics for malnutrition, coagulopathy, ascites, and cholangitis. This management was continued after treatment of common bile duct stones.

In these patients, we studied signs and symptoms, pretreatment complications, stone classification, bile cultures, and cholangiographic findings. Morbidity and mortality rates were compared between the surgery group and the EST group. Clinical data before or during treatment were analyzed to identify factors predictive of significantly increased mortality. The data analyzed were as follows: (1) blood liver chemistry tests, prothrombin times, platelet counts, cholangitis, and Child classification[8] (all before treatment); (2) timing of treatment; and (3) intraoperative hemorrhage.

To provide comparative data, we reviewed 364 noncirrhotic patients treated for choledocholithiasis during the same years to determine intraoperative blood loss and morbidity and mortality rates. Of the 364 patients, 240 were treated with surgery and 124 underwent EST.

Gallstones were classified as pure cholesterol, calcium bilirubinate, black, mixed, or combined stones according to the findings on cross section. Pure cholesterol stones had a radial pattern with a white to light yellow color. Calcium bilirubinate stones had multiple concentric layers with a brown color. Black stones were dark brown or black, friable, and amorphous. These stones mainly contained unconjugated bilirubin[9] and are called "pigment stones" in the United States and Europe. Mixed stones had a pattern of both radial formation and multiple concentric layers. Combined stones had multiple strata of different composition.

Statistical analyses were done using the chi square test and the Student's t test. Differences were considered to be significant when the p value was less than 0.05.

RESULTS

Of the 16 cirrhotic patients with choledocholithiasis, 15 had calcium bilirubinate stones and 1 had mixed stones. All six patients who had common duct bile sampled during surgery had bile cultures that were positive for bacteria: *Escherichia coli* in three, *Klebsiella* in two, *Citobacter* in two, and *Bacteroides* in one.

On endoscopic retrograde cholangiogram or intraoperative cholangiogram, the mean diameters of the common bile duct and the proximal part of the left main hepatic duct were 15 mm (range, 9 to 25 mm) and 5 mm (range, 4 to 9 mm), respectively.

On admission for the treatment of gallstones, 12 (75%) of these 16 patients had signs and symptoms of choledocholitiasis (abdominal pain, jaundice, and fever) (Table 1). In addition, three had ascites and three had a psychological disorder. Four had acute nonsuppurative cholangitis and three had acute obstructive suppurative cholan-

Address reprint requests to Masanori Sugiyama, M.D., First Department of Surgery, Tokyo University School of Medicine, 7-3-1, Hongo, Bunkyo-ku, Tokyo 113, Japan.

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Table 1. SIGNS AND SYMPTOMS OF 16 CIRRHOTIC PATIENTS WITH COMMON BILE DUCT STONES

Symptom	No. of Patients	
	Previous	On Admission
Abdominal pain	14	8
Jaundice	14	11
Fever	10	7
Ascites	7	3
Psychologic disorder	4	3
Asymptomatic	1	4

Table 3. OUTCOMES OF SURGICAL TREATMENT FOR COMMON BILE DUCT STONES

Outcome	Cirrhotic Patients (n = 9)	Noncirrhotic Patients (n = 240)	
Mortality (%)	4 (44.4)	3 (1.3)	$p < 0.01$
Morbidity (%)	6 (66.7)	18 (7.5)	$p < 0.01$
Intraoperative blood loss in mL (mean ± SD)	1576 ± 602	330 ± 173	$p < 0.05$

gitis (AOSC)[10] (Table 2). Before admission, 15 (94%) of the 16 patients had had symptoms related to the biliary tract (Table 1).

Cholangitis, even nonsuppurative, was not completely improved by medication in any of the cases. Consequently, emergency or early biliary decompression was performed in these cases.

During surgery for choledocholithiasis, the mean blood loss was 1576 mL (range, 545 to 2600 mL) in cirrhotic patients (Table 3): 873 mL in Child A, 1770 mL in Child B, and 1780 mL in Child C. The mean hemorrhage was 1317 mL in patients with a prothrombin time level greater than 40%, and 1900 mL in patients with a prothrombin time level less than 40%. The mean blood loss measured 1095 mL in patients with platelet counts greater than 100,000/mm^3, and 1817 mL in patients with platelet counts less than 100,000/mm^3. Excessive hemorrhage occurred from the gallbladder bed, Calot's triangle, or choledochotomy site. The mean blood loss was significantly greater in cirrhotic patients than in noncirrhotic patients (330 mL).

In the surgery group, four patients died while hospitalized for a mortality rate of 44.4% (Tables 3 and 4). One died of intraperitoneal hemorrhage and liver failure on postoperative day 31, one of hepatorenal failure on postoperative day 16, one of intraperitoneal abscess, sepsis, and liver failure on postoperative day 43, and one of upper gastrointestinal hemorrhage and liver failure on postoperative day 21. The mortality rate was 25% (one of four) in patients with operative hemorrhage less than 1500 mL, and 60% (three of five) in patients with operative hemorrhage greater than 1500 mL. Two of the four patients who died had ascites at surgery and continued leakage of ascitic fluid from the drain site after operation, despite the administration of diuretics. In addition to the deaths, two patients had complications: one had T-tube dislocation due to ascites, local biliary peritonitis, and transient coma, and one had deterioration of liver dysfunction.

Table 2. COMPLICATIONS BEFORE TREATMENT OF 16 CIRRHOTIC PATIENTS WITH COMMON BILE DUCT STONES

Complication	No. of Patients
Acute cholangitis	7
Acute pancreatitis	0
Acute cholecystitis	0
Esophageal varices	6
Hepatocellular carcinoma	0
Diabetes mellitus	4

All seven patients safely and successfully underwent EST followed by stone extraction (Table 5). None had complications related to the EST procedures. However, one died of liver failure 39 days after successful stone removal. After he underwent EST with a serum bilirubin level of 19.5 mg/dL, a serum albumin level of 2.0 g/dL, ascites, and fever, he experienced jaundice without cholangitis. He was considered to have liver failure at the time EST was performed.

The overall mortality rate was 31.3% (5 of 16) in cirrhotic patients. This rate was significantly higher than in noncirrhotic patients (0.8%, 3 of 364) (Tables 3 and 5). Pretreatment clinical data were comparable between the surgery group and the EST group in cirrhotic patients (Table 4). The mortality rate was significantly higher in the surgery group (44.4%, four of nine) than in the EST group (14.3%, one of seven). The morbidity rate was significantly higher in the surgery group than in EST group (66.7% *vs.* 14.3%). After surgical treatment, cirrhotic patients had significantly higher mortality and morbidity rates (44.4% and 66.7%, respectively) than noncirrhotic patients (1.3% and 7.5%, respectively) (Table 3). There was a significant difference in mortality rate (14.3% *vs.*

Table 4. FACTORS AND MORTALITY RATES ON CIRRHOTIC PATIENTS WITH COMMON BILE DUCT STONES

Factor	Surgery (Death/Total)*	EST (Death/Total)	Both (Death/Total)
Total	4/9	1/7	5/16
Total bilirubin level (mg/dL)			
≤2	0/3	0/2	0/5
2–5	0/2	0/1	0/3
≥5	4/4	1/4	5/8
Serum glutamic oxalacetic transaminase level (units)			
≤35	0/2	0/2	0/4
36–99	1/3	0/3	1/6
≥100	3/4	1/2	4/6
Serum albumin level (g/dL)			
≥3.5	1/3	0/2	1/5
3.0–3.5	1/3	0/1	1/4
≤3.0	2/3	1/4	3/7
Prothrombin time (%)			
≥80	0/2	0/3	0/5
40–80	1/3	0/2	1/5
≤40	3/4	1/2	4/6
Platelet count ($\times 10^4/mm^3$)			
≥20	0/1	0/1	0/2
10–20	0/2	0/3	0/5
≤10	4/6	1/3	5/9
Child classification			
A	0/2	0/1	0/3
B	0/2	0/1	0/3
C	4/5	1/5	5/10
Cholangitis			
Absent	0/5	0/4	0/9
Nonsuppurative cholangitis	2/2	1/2	3/4
AOSC	2/2	0/1	2/3
Timing of treatment			
Elective	1/6	0/5	1/11
Emergent	3/3	1/2	4/5

* Cases of hospital death cases/total cases.

0%) between cirrhotic and noncirrhotic patients who underwent EST, but there was no difference in morbidity rate (14.3% *vs.* 6.5%) (Table 5).

For the 16 cirrhotic patients with choledocholithiasis, the following factors, before or during treatment, were associated with significantly increased mortality rates: a total bilirubin level greater than 5 mg/dL, a serum glutamic oxalacetic transaminase level greater than 100 units, a prothrombin time less than 40%, a platelet count less than 100,000/mm^3, Child C classification, nonsuppurative cholangitis or AOSC, and emergency surgery or EST (Table 4). These factors tended to increase mortality rates in the surgery group also, but not significantly.

DISCUSSION

The incidence of cholelithiasis in patients with liver cirrhosis is reported to be twice that of the noncirrhotic population.[1,2] Gallstones in cirrhotic patients are most often black stones[1,2] ("pigment stones"). Black stones are predominantly located in the gallbladder in both cirrhotic[1] and noncirrhotic[11] patients. Compared with noncirrhotic patients, cholelithiasis in cirrhotic patients is mostly asymptomatic and has a lower incidence of complications[3,4] that include acute cholecystitis, obstructive jaundice, cholangitis, and acute pancreatitis. In our series of common bile duct stones, 94% of patients had calcium bilirubinate stones. Calcium bilirubinate stones are not commonly seen in the United States, but are the most common type of stones in noncirrhotic patients with choledocholithiasis in Japan.[11] These stones are associated with bacterial infection of the biliary tract.[12] Although liver cirrhosis causes black stones to occur in the gallbladder, choledocholithiasis and cirrhosis might coexist in our series, which did not include cases of biliary cirrhosis, from a viewpoint of stone classification. Choledocholithiasis has higher incidences of symptoms and complications than cholecystolithiasis in noncirrhotic patients. Similarly, 94% of cirrhotic patients with choledocholithiasis had biliary tract symptoms such as abdominal pain, jaundice, and fever. Acute cholangitis and AOSC accompanied 44% and 19% of these patients, respectively.

In noncirrhotic patients, even asymptomatic common bile duct stones are relative indications for treatment because of the high possibility of complications. Also, almost all cirrhotic patients with choledocholithiasis, even if asymptomatic, should be treated because obstructive jaundice or cholangitis often causes liver failure.

Many reports established high risk, including major intraoperative hemorrhage and high morbidity and mortality rates, in biliary surgery for cirrhotic patients.[3–6] In

Table 5. OUTCOMES OF EST FOR COMMON BILE DUCT STONES

Outcome	Cirrhotic Patients (n = 7)	Noncirrhotic Patients (n = 124)	
Success in stone extraction (%)	7 (100.0)	120 (96.8)	NS
Mortality (%)	1 (14.3)	0	$p < 0.01$
Morbidity (%)	1 (14.3)	8 (6.5)	NS

this study, cirrhotic patients had greater blood loss in surgical treatment for choledocholithiasis than noncirrhotic patients. The volume of hemorrhage was related to the Child classification of hepatic functional reserve. One of the reasons for excessive hemorrhage was the development of large collaterals in the gallbladder bed, Calot's triangle, and hepatoduodenal ligament due to portal hypertension. Coagulopathy and thrombocytopenia also caused excessive blood loss, including major oozing from the incision and raw peritoneal surface. Coagulopathy and liver dysfunction should be corrected by preoperative and postoperative intense medical management including the administration of fresh frozen plasma.[13] However, this management cannot necessarily preclude massive bleeding. Local hemostatic agents such as microfibrillar collagen or vasoconstrictive agents such as vasopressin should be considered.[14] Cholecystolithotomy,[3] cholecystostomy,[5] or subtotal cholecystectomy[15] with the posterior wall left intact were advised for gallbladder stones in cirrhotic patients to avoid massive bleeding from the gallbladder bed.

The mortality rate was reported to be as high as 10% to 25% in surgical treatment of gallstones in cirrhotic patients.[3,5,6,13] Surgical treatment of choledocholithiasis in cirrhotic patients had high morbidity and mortality rates of 66.7% and 44.4%, respectively. The common causes of death were liver failure, postoperative hemorrhage (intraperitoneal or upper gastrointestinal), and sepsis. All deaths resulted from liver failure. Surgical procedures performed on the liver and biliary tract, anesthesia, and excessive intraoperative blood loss tended to exacerbate liver dysfunction because these cirrhotic patients did not have hepatic functional reserve. Cirrhotic patients were also susceptible to infection. Ascites leakage was a characteristic complication after biliary surgery in cirrhotic patients. In one of three patients with ascites leakage, T-tube dislocation due to ascites resulted in biliary peritonitis.

Factors that increased the surgical mortality rate were preoperative liver dysfunction, preoperative cholangitis, emergency surgery, and massive intraoperative blood loss. The increased mortality rate often reflected the degree of hepatic decompensation, which was indicated by abnormal blood liver test results (serum albumin, total bilirubin, and serum glutamic pyruvic transaminase values), prolonged prothrombin time, thrombocytopenia, and the presence of ascites. The surgical mortality rate was 0% in Child A and B and 80% in Child C. Acute cholangitis often resulted in the deterioration of liver function and general condition in cirrhotic patients. Acute cholangitis, if resistant to Antibiotics, requires early biliary decompression in noncirrhotic patients.[10] Emergency decompression is especially indicated for AOSC. Because surgical decompression in AOSC is associated with a high mortality rate, a nonsurgical approach such as percutaneous transhepatic biliary drainage (PTBD), EST, or ENBD is recommended.[15] The administration of antibiotics could not improve even nonsuppurative cholangitis in cirrhotic patients. Surgical decompression in these patients was associated with a mortality rate of 100%. PTBD was difficult to perform in cirrhotic patients because of liver atrophy and low-grade dilatation of the intrahepatic tree. Dilatation of the proximal part of the left hepatic duct, which was usually punctured in PTBD, was not sufficient to perform PTBD, despite moderate to severe dilatation of the extrahepatic duct. PTBD is contraindicated for patients with ascites. However, EST was safely performed and improved cholangitis in cirrhotic patients. Even patient with ascites underwent EST without complications. Because emergency cases were often accompanied by severe cholangitis and excluded preparation to improve the liver function and general condition, emergency cases had a high mortality rate. Excessive intraoperative bleeding[6] caused the deterioration of liver function and led to liver failure.

The EST group, which had liver dysfunction and coagulation disturbance comparable to those of the surgery group, had no complications related to endoscopic procedures; however, one death occurred (14.3%). The cause of death was considered to be preexisiting liver failure. These results were better than those from surgical treatment. EST caused only minimal stress for these high-risk patients and avoided the risk of major hemorrhage during treatment. Although coagulopathy is presented as a risk factor for bleeding after EST,[16] the practical criteria are not well documented. In our series, even patients with severe coagulopathy and liver decompensation underwent EST safely. However, these abnormalities should be corrected before EST, if possible. In extremely critical cases requiring emergency biliary decompression, it might be safer to initially perform ENBD alone without sphincterotomy, although we did not experience such situations. In these cases, common duct stones should be extracted by EST after liver function and general condition are improved. In general, EST is established as a first-choice treatment for common duct stones in elderly, postcholecystectomy patients at high risk. Patients with liver cirrhosis, particularly those with decompensated liver disease (Child C), should be treated with EST because EST is less invasive and safer than surgical treatment. Because of a low incidence of cholecystitis after EST,[16] subsequent cholecystectomy is unnecessary in most cirrhotic patients at high surgical risk, especially in patients without gallbladder stones.

In cirrhotic patients, common bile duct stones often cause liver dysfunction resulting in hepatic failure and

making the general condition worse as a result of extrahepatic biliary obstruction or retrograde cholangitis. Therefore, almost all cases of choledocholithiasis with cirrhosis, even if asymptomatic, are indications for treatment, despite the high risk. Child C cases have a very poor outcome after surgery or EST. It is safer to treat gallstones after improvement of Child C to Child A or B. Hepatic dysfunction, coagulation disturbance, and cholangitis should be improved before the treatment of gallstones, except in emergency cases such as AOSC. EST is recommended as the first-choice treatment for choledocholithiasis in cirrhotic patients because of its effectiveness and safety.

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