

ORIGINAL ARTICLE

Percutaneous Transhepatic Cholangiography and Drainage is an Effective Rescue Therapy for Biliary Complications in Liver Transplant Recipients Who Fail Endoscopic Retrograde Cholangiopancreatography

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Background: We attempted to evaluate both the factors that predispose a patient to biliary complications after liver transplantation and the results of percutaneous transhepatic cholangiography and drainage (PTCD) for the management of those complications.

Methods: This study retrospectively reviewed the cases of 81 patients who received liver transplants at Taipei Veterans General Hospital between February 2003 and June 2008. Biliary complications were diagnosed on the basis of clinical findings, laboratory data, and the results of imaging studies.

Results: A total of 18 patients (22.2%) developed biliary complications, and living donor liver transplantation (LDLT) was a significant risk factor ($p = 0.035$), compared to cadaveric liver transplantation. Eight patients with biliary complications received PTCD as the first treatment modality and 6 had successful results. An additional 10 patients received endoscopic retrograde cholangiopancreatography (ERCP) initially, but only 2 patients were effectively managed. One patient received conservative treatment after ERCP failure. One patient died from sepsis after ERCP. The remaining 6 patients with failed ERCP were successfully managed with PTCD. The overall mortality rate in these patients with biliary complications was 16.7%. No significant prognostic predictors were identified, including age, sex, biochemical data, and model for end-stage liver disease scores.

Conclusion: Biochemical markers cannot predict biliary complications preoperatively. LDLT increases the risk of biliary complications. PTCD is an effective rescue therapy when ERCP fails. [*J Chin Med Assoc* 2009;72(8):395–401]

Key Words: biliary tract, cholangiography, liver transplantation

Introduction

Biliary complications are common after liver transplantation and can cause significant morbidity and mortality.^{1,2} The incidence of biliary complications after liver transplantation has been reported to affect from 10% to 30% of liver transplant patients.³ Such complications include stricture, leakage, casts, sludge,

stones, and sphincter of Oddi dysfunction.⁴ Strictures and leaks are the most common biliary complications after liver transplantation. The incidence in cadaver liver transplantation has been reported to be less than 10%, but it can be up to 30% in living donor liver transplantation (LDLT).^{3,5–8} Biliary strictures can be classified into anastomotic strictures (AS) and non-anastomotic strictures (NAS). Anastomotic stricture



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is caused by technical factors such as uneven distribution or tension of the sutures. Nonanastomotic stricture is due to immunologic and ischemic factors, and graft loss.⁴ The 2 types of strictures cannot be compared because of inherent differences in their pathology, time to presentation, treatment, and response to treatment.⁴

LDLT was first performed by Nagasue et al in Japan in 1989.⁹ Despite improvements in surgical techniques, development of immunosuppressive drugs, and better organ preservation, the rate of biliary complications remains unchanged.^{10,11} Biliary complication management includes a combination of endoscopic, radiologic and surgical procedures.¹² Endoscopic management of AS is successful in 70–100% of cases; however, with NAS, the rate of success drops to 50–75%.⁴ In LDLT, the success rate is 60–75% for patients with AS and 25–33% for those with NAS.⁴ Percutaneous transhepatic drainage is considered to be second-line treatment for biliary complications after endoscopic retrograde cholangiopancreatography (ERCP) failure.

We retrospectively reviewed the patients and evaluated: (1) the factors that predispose patients to develop biliary complications after liver transplantation; and (2) the effectiveness of percutaneous transhepatic cholangiography and drainage (PTCD) or ERCP for the management of these complications.

Methods

Patients

We retrospectively reviewed the chart records of consecutive patients who received liver transplantation in the Division of General Surgery at Taipei Veterans General Hospital between February 2003 and June 2008. A total of 81 cases of adults who received liver transplants during that time were included in the study.

Biliary complications were suspected when: (1) there was at least 1 clinical finding (fever, leukocytosis, abdominal pain, peritonitis, cholangitis, sepsis); (2) the drainage tube showed biliary staining; or (3) abdominal sonography, computed tomography (CT), ERCP, or magnetic resonance cholangiopancreatography revealed a problem, including biliary tract dilatation, stricture, or leakage. Suspected complications were then confirmed by PTCD or ERCP.

ERCP method

All patients receiving ERCP were mildly sedated. After receiving a 10-mL simethicone drop, 8% lidocaine was locally sprayed into the back of the patient's throat.

Patients then received 40 mg intramuscular injection of hyoscine-N-butylbromide (Buscopan®; Boehringer Ingelheim GmbH, Ingelheim, Germany). Then, a side-view endoscope (JF-260; Olympus, Tokyo, Japan) was passed into the descending duodenum and selective cannulation with a 5-Fr cannula (PK-109Q-1; Olympus) was performed. Cholangiograms and pancreaticograms were obtained by injecting contrast into the common bile duct and pancreatic duct, respectively, under fluoroscopy.

When bile leakage was detected, use of a nasobiliary catheter (NBC) was indicated. A 0.025-inch, 450-cm microinvasive Teflon®-coated guidewire (Hydra Jagwire® Guidewire; Boston Scientific, Boston, MA, USA) with a 3-cm flexible tip was inserted via the cannula into the common bile duct. After withdrawal of the cannula over the guidewire, a 6.5-Fr NBC (ENBD-6.5-LEUNG-7; Cook Inc., Bloomington, IN, USA) was inserted into the biliary system over the guidewire. The endoscope was removed gradually without displacing the catheter.

If the cholangiogram revealed biliary stricture, biliary stenting was considered. When indicated, a stent was placed after balloon dilatation; 1 or 2 8.5-Fr plastic stents (Flexima™ Biliary Stent System; Boston Scientific) were then inserted.

PTCD method

Under sonographic guidance, we directly punctured the intrahepatic duct with a 22-gauge Chiba needle (Cook Inc.) via a right intercostal approach. Then, cholangiography was performed, and anastomotic stricture or leakage was identified. A 0.018-Fr guidewire was inserted through the Chiba needle, and then we dilated the tract with a 4-Fr dilator. Next, we introduced a 4-Fr KMP catheter (Cook Inc.) and negotiated through the stricture with a 0.035-Fr stiff guidewire (Terumo Corp., Tokyo, Japan). Next, the tract was dilated with a 9-Fr dilator, and an 8-Fr angiosheath (Cordis Corp., Miami, FL, USA) was introduced into the bile duct with the tip just distal to the anastomotic stricture. We dilated the narrow segment with a 5- to 40-mm ATB balloon catheter (Cook Inc.) and then inserted an 8.3-Fr 32 side-hole ring catheter (Cook Inc.) with its tip crossing the stenosis in the distal common bile duct.

PTCD revision was performed after 2 weeks. The original tract was confirmed and an 8-Fr angiosheath was advanced and the narrowed segment was dilated with an 8- to 40-mm ATB balloon catheter. After dilatation, the 12-Fr silicone catheter could be advanced smoothly to the tip of the distal common bile duct. If no catheter-related abdominal pain was found, once

or twice a week, an ever-larger catheter was inserted, until a 20-Fr silicone catheter could be inserted.

Follow-up

Serum aspartate aminotransferase, alanine aminotransferase, total bilirubin and alkaline phosphatase levels were measured prior to the procedures, and patients were followed up once or twice a week, depending on their condition. After they were discharged from the hospital, they were followed in our outpatient department every 2–4 weeks, again depending on their condition. All ERCP image files were reviewed by 1 gastroenterologist. All PTCD procedures were performed and reviewed at our hospital by the same radiologist. The surgeon decided whether to perform ERCP or PTCD on an individual basis when biliary complications first occurred. The first case of biliary complication, managed by PTCD, was performed in April 2003. Before March 2006, PTCD was the first consideration for the management of biliary complications after liver transplantation. After we reviewed studies in the field, we decided that ERCP would be

the treatment of choice for these patients. Now, ERCP is used first to manage biliary complications in our hospital.

Statistical analysis

Statistical analyses were performed using the χ^2 test and independent *t* test, where appropriate. A *p* value < 0.05 was considered statistically significant. All analyses were performed with SPSS version 12.0 (SPSS Inc., Chicago, IL, USA) for Windows.

Results

A total of 81 adult patients received liver transplantation in our hospital (Table 1). We reviewed all the patients' medical records and found that 49.4% of patients had received LDLT. After liver transplantation, 18 (22.2%) patients developed biliary complications (Figure 1). The characteristics of the 18 patients are shown in Table 2. The mean age was 53.6 years. The most common reason for liver transplantation

Table 1. Factors correlated with biliary complications before liver transplantation*

Parameters	Patients without biliary complications (n = 63)	Patients with biliary complications (n = 18)	<i>p</i>
Age (yr)	51.5 ± 11.3	53.6 ± 8.9	0.481
Sex (male:female)	38:25	13:5	0.518
Albumin	3.0 ± 0.5	3.2 ± 0.6	0.201
Creatinine	1.5 ± 1.2	1.1 ± 0.4	0.215
Total bilirubin	6.7 ± 9.0	10.2 ± 10.9	0.174
Prothrombin time (INR)	1.4 ± 0.5	1.7 ± 0.8	0.150
MELD score	17.9 ± 8.0	19.7 ± 8.5	0.418
Donor-to-recipient ratio (living:cadaver)	27:36	13:5	0.035

*Data expressed as mean ± standard deviation or *n*. INR = international normalized ratio; MELD = Model for End-stage Liver Disease.

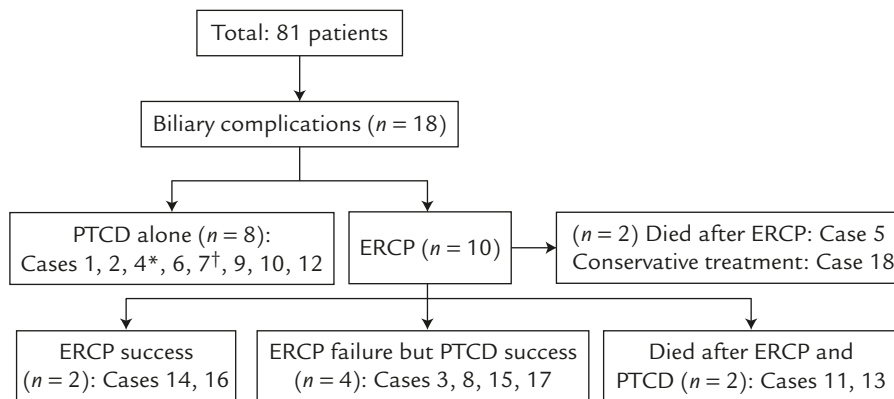


Figure 1. Courses of the 18 patients who had biliary complications. *The 4th case received long-term PTCD implantation because 1 branch of the bile duct was totally ligated during operation; †the 7th patient received conservative treatment after PTCD failure. PTCD = percutaneous transhepatic cholangiography and drainage; ERCP = endoscopic retrograde cholangiopancreatography.

Table 2. Characteristics of the 18 patients with biliary complications after liver transplantation

No.	Sex	Age (yr)	MELD score	Operation cause	Donor	Complication	Method	Cause of death
1	F	61	26.2	HBV with LC	LDLT	AS	PTCD	
2	F	43	15.0	Secondary biliary cirrhosis	LDLT	AS	PTCD	
3*	F	61	10.9	HCV + HCC	LDLT	Leak	ERCP → PTCD	
4*	F	60	22.8	HBV with LC	LDLT	Leak + total occlusion	PTCD	
5	F	62	16.6	HCV with LC	LDLT	Leak	ERCP	Sepsis
6	M	42	18.5	HBV + HCC	Cadaver	AS	PTCD	
7	M	60	34.1	HBV + HCV	LDLT	AS + NAS	PTCD → Con	
8*	M	60	19.0	HBV + HCC	LDLT	Leak + AS	ERCP → PTCD	
9	M	37	35.3	Fulminant hepatitis (HBV)	Cadaver	AS	PTCD	
10	M	45	18.4	HCV + HCC	LDLT	Leak	PTCD + operation	
11*	M	44	15.0	HCV with LC	LDLT	Leak + AS	ERCP → PTCD	HCV hepatitis
12	M	61	9.6	HBV with LC	Cadaver	AS	PTCD	
13*	M	48	32.0	HBV with LC	Cadaver	AS	ERCP → PTCD	Graft rejection
14	M	45	28.2	Fulminant hepatitis (HBV)	LDLT	Leak	ERCP [†]	
15*	M	66	17.5	HBV + HCC	LDLT	AS	ERCP → PTCD	
16	M	53	10.4	HBV with LC	LDLT	Leak + AS	ERCP [†]	
17*	M	60	6.4	HBV + HCC + cholangiocarcinoma	Cadaver	Leak + AS	ERCP → PTCD	
18*	M	56	18.6	HBV + HCC	LDLT	Leak	ERCP → Con	

*ERCP failure cases (see Table 3); [†]the patient received ERCP with nasobiliary catheter insertion; [‡]the patient received ERCP with plastic stent insertion. F = female; M = male; HBV = hepatitis B virus; LC = liver cirrhosis; HCV = hepatitis C virus; HCC = hepatocellular carcinoma; LDLT = living donor liver transplantation; AS = anastomotic stricture; NAS = non-anastomotic stricture; PTCD = percutaneous transhepatic cholangiography and drainage; ERCP = endoscopic retrograde cholangiopancreatography; Con = conservative treatment.

among these patients was chronic hepatitis-related liver cirrhosis. The interval between transplantation and development of complications was defined as the time from the operation date to the date of ERCP or PTCD. This interval could be as short as 1.4 weeks or as long as 77.7 weeks. The most common finding on imaging was anastomotic stricture, followed by biliary leakage.

We managed all these patients with the procedures as shown in Figure 1. When biliary complications were found, the surgeon in charge determined the initial intervention treatment. Some patients received ERCP first. If ERCP failed, PTCD was arranged.

Eight patients received PTCD initially, and 6 cases were successfully managed. Among those 6 patients, the PTCD was removed after biochemical data returned to normal and no stricture or leakage was found on cholangiography.

Ten patients received ERCP initially. ERCP was attempted but failed in the 18th patient due to severe pyloric stenosis. After conservative treatment, no complication was found after the abdominal drainage tube was removed. The 5th patient was diagnosed with bile

leakage noted on ERCP and died from sepsis not related to ERCP. The 14th and 16th patients were successfully managed with ERCP alone. The 14th patient was diagnosed with anastomotic bile leak by ERCP, and an NBC was inserted. The NBC was removed smoothly without any complications. The 16th patient was diagnosed with anastomotic stricture and leak by ERCP. A plastic stent was inserted, and he was discharged smoothly without any complications.

After ERCP failed, PTCD was arranged, and the biliary complications in 4 patients (Cases 3, 8, 15, and 17) were successfully managed. These patients were all successfully managed after receiving PTCD treatment. The drainage tubes were successfully inserted in the 11th and 13th patients. However, both died, due to hepatitis C virus reactivation and graft rejection, respectively.

The overall mortality rate in these patients with biliary complications after liver transplantation was 16.7%. We analyzed the characteristics of the patients with biliary complications (Table 2). Biochemical data, including Model for End-stage Liver Disease scores, cannot predict biliary complications after liver transplantation.

Table 3. Causes of endoscopic retrograde cholangiopancreatography (ERCP) failure

Case	ERCP failure causes	Rescue management	Result
3	Guidewire could not pass the anastomotic stricture	PTCD	A
8	Surgical repair was suggested due to severe leakage and AS	PTCD	A
11	Prolonged use of NBC, then PTCD was inserted	PTCD	D*
13	Angulation over bile duct anastomosis	PTCD	D†
15	Total occlusion of the bile duct	PTCD	A
17	Guidewire could not pass the anastomotic stricture	PTCD	A
18	Endoscope could not pass due to severe pyloric deformity	Conservative treatment	A

*Died after reactivation of hepatitis C virus; †died after graft rejection. AS = anastomotic stricture; NBC = nasobiliary catheter; PTCD = percutaneous transhepatic cholangiography and drainage; A = alive; D = dead.

Only LDLT was a risk factor of biliary complication after liver transplantation ($p=0.035$).

Discussion

LDLT is more common in Taiwan than in Western countries, largely due to cultural differences. In our study, 49.4% of patients received LDLT (Table 1). Biliary complications are common after a liver transplant.¹³ Many studies have attempted to identify predisposing factors and new ways to avoid and to resolve such complications. Eighteen patients with biliary complications were found after we retrospectively reviewed their medical charts (Figure 1).

In a study by Qian et al, preoperative serum bilirubin levels and living donor liver grafts were found to be independent risk factors of biliary complications after liver transplantation.¹⁴ Others have reported conflicting results.¹⁵ Biochemical markers cannot be used to predict biliary complications after liver transplantation (Table 1). Our data revealed that LDLT is a risk factor for biliary complications ($p=0.035$). The most common cause of biliary complication is anastomotic stricture (Table 2). The relatively short length and small diameter of the living donor bile duct result in technical difficulties and a higher rate of anastomotic stricture.

Although 1 center demonstrated excellent results with surgical management alone for treatment of biliary complications,¹⁶ ERCP before surgery is still the first choice for managing biliary complications after liver transplantation due to its noninvasive nature.^{17,18} Surgical intervention is the treatment of choice for significant biliary anastomotic disruptions, massive biliary leaks, or any biliary complication associated with severe intra-abdominal or systemic infection.¹⁹

Most biliary complications after liver transplantation can be appropriately managed with ERCP.^{20,21} However, a significant number of patients need other

approaches.²² PTCD may be the first choice of rescue therapy because of its high success rate.²³ All the ERCP failures in our study are shown in Table 3. Severe anastomotic stricture was the most common cause of ERCP failure in our hospital (Table 3). When the anastomotic stricture is severe, the ERCP guidewire is difficult to cannulate through the anastomotic stricture, as has been shown in previous studies.¹⁸ Therapeutic procedures cannot be performed because the operator is unable to pass the guidewire through the stenotic site. When severe anastomotic leaks are combined with anastomotic stricture, surgical repair is suggested. The higher rate of LDLT, which is more common in Taiwan than in Western countries, also contributes to the higher rate of ERCP failure. In this retrospective study, the first case of biliary complication, managed by PTCD, was performed in April 2003. After March 2006, ERCP became the first choice for therapy of biliary complications. However, ERCP is a relatively difficult procedure, requiring a longer learning curve. In addition, the limited number of cases and lack of experience with using ERCP after liver transplantation may have contributed to the high failure rate at our hospital.

It is difficult to use ERCP to treat patients who have previously undergone hepaticojejunostomy. In a recent study, PTCD was reported to be an effective alternative treatment for post-hepaticojejunostomy stricture following LDLT.²⁴ In our experience, most of the intrahepatic bile ducts were not dilated when biliary complications were diagnosed. The absence of enlarged intrahepatic biliary ducts should not be a contraindication to PTCD.²⁵ Eight patients received PTCD initially, and 6 of these patients had successful implantations (Figure 1). Six ERCP-failed patients received PTCD, and the procedure was successful in 4 of these patients. The drainage tubes were successfully inserted in the remaining 2 patients; unfortunately, they died after hepatitis C virus reactivation and graft rejection, respectively. From a recent study,

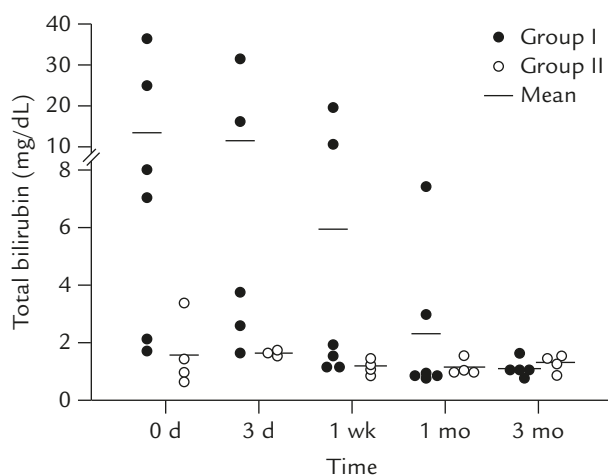


Figure 2. A comparison of total bilirubin levels between patients who received PTC initially (Group 1) or after ERCP failure (Group 2). Group 1 included Patients 1, 2, 6, 9, 10 and 12. Group 2 included Patients 3, 8, 15 and 17.

PTCD may serve as a successful rescue procedure in failed cases of endoscopic therapy for post-LDLT biliary stricture.²³ Our experience disclosed a high success rate of initial treatment and rescue therapy after endoscopic treatment failure in liver transplantation-related biliary complication.

When we compared the total bilirubin levels between patients who received PTC initially (group 1) or after ERCP failure (group 2), there was no significant difference in recovery between the 2 groups after 3 months (Figure 2). In group 1, the 6th and 10th patients had extremely high baseline total bilirubin levels. The 6th patient underwent liver transplantation in March 2003. Because we had less experience in the management of biliary complications, PTC was arranged until abdominal sonography revealed dilatation of the intrahepatic ducts. The 10th patient had narrowing of the portal vein with liver function impairment after liver transplantation. Bile stain was found in the external drainage tube and total bilirubin level was increased from 9.8 mg/dL to 29.5 mg/dL in 1 week. Then, biliary leakage and stenosis were diagnosed. PTC was successfully inserted and exploratory laparotomy with abscess debridement was also performed on the same day.

In our study, 22% of the liver transplant recipients had biliary complications. Biochemical markers, including Model for End-stage Liver Disease score, could not predict biliary complications preoperatively. LDLT poses a higher risk of biliary complications. PTC is an effective rescue method for managing biliary complications if ERCP has failed. Finally, when determining the best approach for managing patients

with biliary complications, the experience of the staff and available facilities in each transplant center should be considered.

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