Int Surg 2019;**104:**27–32
DOI: 10.9738/INTSURG-D-17-00134.1

Efficacy of a Biliary Splint at the Anastomosis in Living Donor Liver Transplantation—With a Special Reference to Postoperative Endoscopic Treatment for Biliary Stricture

Satomi Okada, Akihiko Soyama, Masaaki Hidaka, Tomohiko Adachi, Shinichiro Ono, Koji Natsuda, Takanobu Hara, Mitsuhisa Takatsuki, Susumu Eguchi

Department of Surgery, Nagasaki University Graduate School of Biomedical Sciences

Objective: For successful biliary anastomosis in living donor liver transplantation (LDLT), the efficacy of a biliary splint at the anastomosis remains controversial. In the case of biliary anastomotic stricture (BAS), endoscopic intervention is mostly performed as the initial treatment. In this study, we evaluated the efficacy of endoscopic treatment for BAS in patients with placement of splints.

Methods: A retrospective study was conducted with 148 adult patients who underwent LDLT with duct-to-duct biliary anastomosis from 2005 to 2015. A biliary splint was placed in all cases; the splint was removed 3 months after the LDLT. Patients who postoperatively underwent endoscopic treatment for BAS were divided into successful and failed groups.

Results: A total of 24 patients (16.2%) underwent endoscopic treatment postoperatively. The successful group included 14 patients (63.6%) and the failed group included 8 (36.4%). Comparison between the 2 groups in terms of demographic, pretransplant, intraoperative, and posttransplant data did not show any significant differences. Two patients developed BAS within 3 months after LDLT. In these 2 patients, the splint was dislocated, and endoscopic intervention was not successful. Twenty patients developed BAS later than 3 months after LDLT. In contrast to the success rate of endoscopic intervention of 73.3% in patients without splint dislocation ($n = 15$), it was 60% in the patient with dislocation of the splint ($n = 5$).

Corresponding author: Satomi Okada, MD, Department of Surgery, Nagasaki University Graduate School of Biomedical Sciences, 1-7-1 Sakamoto, Nagasaki 852-8501, Japan.
Tel.: +81-95-819-7316; Fax: +81-95-819-7319; E-mail: okada_s_1107@yahoo.co.jp

Conclusion: The prevention of early biliary stricture by placing a splint may lead to an improved success rate of endoscopic intervention, since endoscopic intervention was difficult in the cases of early biliary stricture within 3 months.

Key words: Biliary anastomotic stricture – Biliary complication – Biliary splint – Endoscopic retrograde cholangiography – Living donor liver transplantation

Biliary complications after living donor liver transplantation (LDLT), in particular, biliary anastomotic strictures (BAS) remain a major problem that affects the long-term outcome and quality of life.[1] The higher incidence of BAS in LDLT compared with deceased donor liver transplantation used to be explained by devascularization of the bile duct by hilar dissection in donor surgery or technically complicated biliary reconstruction due to small orifices and possible multiple ducts. And also, biliary leakage was reported to play an important role in the formation of BAS. Hence, BAS might result from inflammation and subsequent fibrosis after biliary leakage.[2,3]

Two types of biliary reconstruction methods, duct-to-duct anastomosis and Roux-en-Y hepaticojejunostomy, are widely performed. Duct-to-duct anastomosis is frequently preferred in adult LDLT because of the physiologic continuity of the biliary system, technical advantages of shorter operative time, and easier endoscopic access to the biliary tract.[4,5]

The incidence of biliary stricture was 19% in LDLT recipients in a systematic review reported by Akamatsu *et al* in 2011. However, recent reports still have shown variation in the incidence of BAS. While some institutes have reported the incidence of BAS around 10%, other institutes have reported the incidence more than 30-50%.[3,6,7]

In case of biliary stricture, endoscopic interventions such as balloon dilation and stent deployment are mostly performed as initial interventions because of their less invasiveness.[2,5] However, if endoscopic treatment fails because of unsuccessful cannulation through the duodenal papilla or stricture, percutaneous transhepatic cholangiographic drainage (PTCD) or reoperation is indicated.

For duct-to-duct anastomosis in LDLT, many institutes prefer to place splinting stents over deceased donor liver transplantation; the proportion of splinting stents was reported to be more than 80%.[5] We also intraoperatively place stents at anastomoses in all cases of duct-to-duct reconstruction in LDLT. Although splinting stents are considered useful to anastomose tiny ducts with ensuring the patency of the anastomosis, the efficacy of a biliary splint at an anastomosis to prevent stricture remains controversial.[8,9]

The aims of this study were to clarify the efficacy of biliary splints by evaluating the correlation between placing biliary splints and success rate of endoscopic treatment. We also conducted this study to determine the risk factors in unsuccessful endoscopic treatment for biliary stricture.

Patients and Methods

Patients

Between April 2005 and July 2015, a total of 168 adult recipients underwent LDLT at Nagasaki University Hospital, Japan. We have adopted a duct-to-duct reconstruction as the first option of biliary reconstruction.[10,11] Twenty patients who did not undergo duct-to-duct reconstruction were excluded from this study. A total of 148 recipients with duct-to-duct biliary anastomosis were included in the study, and a biliary splint was placed in all cases. Data were retrospectively collected from patient hospital charts.

Duct-to-duct anastomosis and biliary splint

In donor operation, we routinely perform intraoperative cholangiography prior to bile duct resection.[12] Our policy for recipients who undergo duct-to-duct anastomosis for bile duct reconstruction is to place a biliary splint in the anastomosis to prevent biliary complications. We use a vinyl chloride tube splint 2 mm in diameter with multiple holes, originally used for retrograde transhepatic biliary drainage. It is equipped with a malleable metallic dull-tipped splint at one end. Prior to duct-to-duct biliary anastomosis, the metallic splint of the tube is inserted from the lumen of the recipient's side of the hepatic duct and externalized through the upper edge of the duodenum. Subsequently, duct-to-duct anastomosis is performed with interrupted, 6-0 biodegradable monofilament polydioxanone su-

tures, and the tube is placed inside the graft intrahepatic bile duct for decompression and splinting. After placement, the externalized site of the common bile duct is treated with a purse-string using the same 6-0 suture. In addition, using the serosa of the duodenum, a Witzel-type fistula is made with a running 4-0 biodegradable monofilament polydioxanone suture.

When the serum level of total bilirubin is lower than 3 mg/dL, and negativity for biliary complications and good passage of contrast media to the duodenum are confirmed, the biliary splint is clamped.

At 3 months after the transplant, the splint is removed by the following two-step method. After confirming the absence of biliary complications with a cholangiogram, the stent is removed only up to the outside of the tract made by the Witzel canalization under radiography, followed by a waiting period of usually 1 day, until leakage through the tract ceases. When no bile leakage is confirmed, the splint is removed at the bedside.[13]

Diagnosis of biliary stricture

After discharge from the hospital, all liver transplant recipients were followed up. Liver function was checked at each follow-up visit and clinical signs and symptoms of biliary stricture (skin itching, jaundice, cholangitis, etc.) were recorded. If liver dysfunction and/or any clinical symptoms were present, we performed image examinations such as abdominal ultrasonography, computed tomography, and magnetic resonance cholangiopancreatography. Biliary stricture was defined as uncontrollable clinical symptoms, and/or liver dysfunction in laboratory data, and/or biliary stricture in image examinations.

Treatment of biliary stricture

As an initial intervention for biliary stricture, we perform endoscopic retrograde cholangiography (ERC) with balloon dilatation and a plastic stent. When ERC fails due to unsuccessful cannulation through the biliary anastomosis or duodenal papilla, we perform repeat ERC or PTCD or reoperation. At our hospital, ERC is performed by gastroenterologists; PTCD is performed by radiologists.

In this study, patients who postoperatively underwent ERC were divided into successful and failed ERC groups. The successful ERC group also included patients who underwent repeat ERC. The cases that finally underwent PTCD or reoperation were included in the failed ERC group.

Statistical analysis

Comparison of categorical values was performed using the χ^2 test. Nonparametric continuous values were compared by using the Mann-Whitney U test. Statistical difference was defined as a value of $P < 0.05$.

Results

Among 148 recipients of adult LDLT with duct-to-duct biliary anastomosis, 24 (16.2%) patients postoperatively underwent ERC due to biliary stricture. In this study, 2 cases that had failed cannulation through the duodenal papilla were excluded. The successful ERC group included 14 patients (63.6%) and the failed ERC group included 8 (36.4%). In the failed ERC group, all patients were successfully treated with PTCD. As a result, no cases underwent reoperation.

First, we compared the 2 groups to clarify the clinical risk factors associated with success or failure of endoscopic intervention. In terms of demographic, perioperative data, comparison between the 2 groups did not show any significant differences (Table 1). The two groups also did not show any significant differences in posttransplant data (Table 2). In the failed ERC group, the rate of patients with dislocation of biliary splints within 3 months after LDLT was higher than in the successful ERC group (50% versus 21.4%), but there was no significant difference. Thus, no pretransplant, intraoperative, or posttransplant data showed significant differences.

Next, we evaluated the correlation between biliary splints and the success rate of endoscopic treatment. As noted, our policy is to remove the biliary splint at 3 months after the transplant. However, in some cases, the splint is spontaneously dislocated within 3 months. In our hospital, 26.7% of adult LDLT patients had the spontaneous dislocation of biliary splint within 3 months. Among 22 patients in this study, the rate of patients with dislocation of splint was 31.8% (n = 7). We evaluated whether the duration of biliary splint placement at the anastomosis was relevant to the timing of the need for and outcome of ERC.

We categorized biliary stricture patients into 4 types according to the duration of splint placement and the timing of ERC need (Fig. 1 and Table 3). In type 1, the splint was not dislocated and ERC

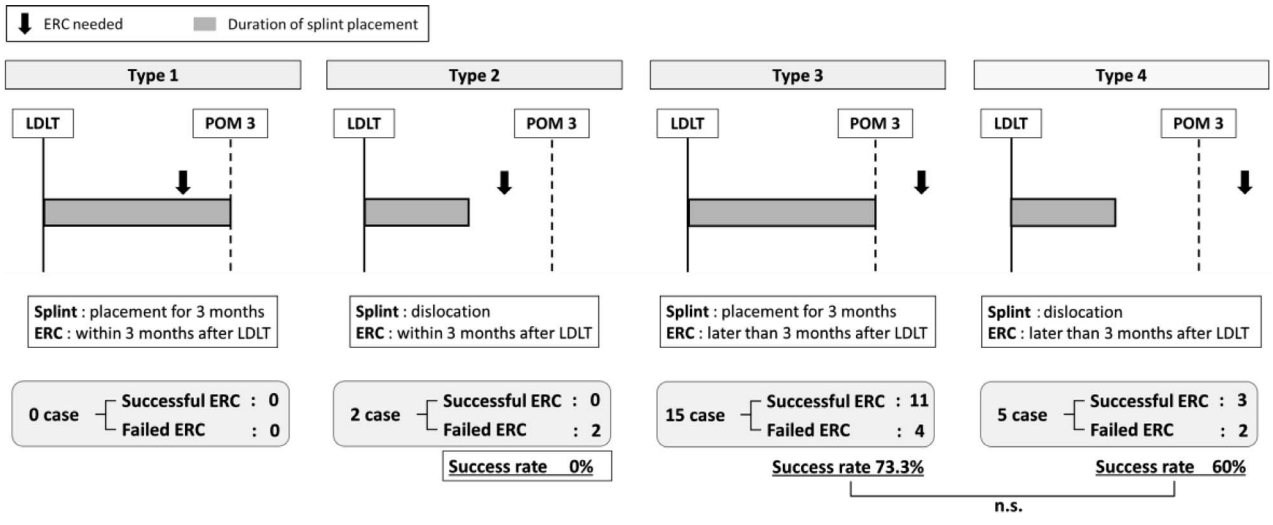
Table 1 Demographic, pretransplant and intraoperative data of the 22 patients with biliary anastomotic stricture

	Successful ERC ($n = 14$)	Failed ERC ($n = 8$)	P
Demographic and pretransplant factor			
Patient age, y	56.5 (33–70)	60 (52–68)	NS
Patient sex, male/female	8/6	5/3	NS
Model for end-stage liver disease score, n (range)	15 (4–27)	13.5 (8–20)	NS
Child-Pugh score, n (range)	9 (5–13)	9 (9–10)	NS
Donor age, y (range)	54.5 (27–65)	50.5 (26–63)	NS
Donor sex, male/female	5/9	2/6	NS
ABO incompatible	6	2	NS
GW/SLV of recipient (%)	38.8	42.9	NS
Graft, right lobe/left lobe	7/7	6/2	NS
Intraoperative factor			
Number of graft bile duct orifices, n (%)			NS
One opening	9 (64.3)	4 (50)	
More than 1 opening	5 (35.7)	4 (50)	
Use of ductoplasty	5 (35.7)	4 (50)	NS
Diameter of bile duct, mm (range)	6 (4–15)	7.5 (2–10)	NS
Blood loss, mL (range)	4,035 (1,120-126,700)	6,270 (1,800–12,900)	NS
Operation time, min (range)	851.5 (598–1,253)	802.5 (701–984)	NS

NS, not significant.

Table 2 Posttransplant data of the 22 patients with biliary anastomotic stricture

	Successful ERC ($n = 14$)	Failed ERC ($n = 8$)	P
Acute cellular rejection, n (%)	1 (7.1)	0 (0)	NS
Cytomegaloviral antigenemia, n (%)	0 (0)	1 (12.5)	NS
Hepatic artery thrombosis, n (%)	0 (0)	0 (0)	NS
Portal vein thrombosis, n (%)	3 (21.4)	1 (12.5)	NS
Timing of ERC needed, n (%)			NS
Within 3 months after LDLT	0 (0)	2 (25)	
Later than 3 months after LDLT	14 (100)	6 (75)	
Dislocation of biliary splint, n (%)	3 (21.4)	4 (50)	NS



＊POM : postoperative month

Fig. 1 Correlation between biliary splints and endoscopic treatment. Biliary stricture patients were categorized into 4 types according to the duration of splint placement and the timing of ERC need.

Table 3 Correlation between biliary splints and endoscopic treatment

	Successful ERC ($n = 14$)	Failed ERC ($n = 8$)	Success rate of ERC, % (M/F)
ERC needed: within 3 months after LDLT	0 (0)	2 (25)	0% (0/2)
Splint: no dislocation (Type 1)	0	0	
Splint: dislocation (Type 2)	0	2	0 (0/2)
ERC needed: later than 3 months after LDLT, n (%)	14 (100)	6 (75)	70 (14/20)
Splint: no dislocation for 3 months (type 3)	11	4	73.3 (11/15)
Splint: dislocation within 3 months (type 4)	3	2	60 (3/5)

intervention was needed within 3 months after LDLT. This type 1 indicates that the biliary splint itself locating at anastomosis may lead to biliary stricture. In this study, there were no patients in type 1. In type 2, the splint was dislocated and ERC intervention was needed within 3 months after LDLT. Two patients were included in type 2. In these 2 patients, ERC intervention failed, and the success rate of ERC in type 2 was 0%. In type 3 and 4, ERC was needed later than 3 months after LDLT. In type 3 and 4, a total of 20 patients developed biliary stricture later than 3 months after LDLT, and 14 were successfully treated with ERC. Thus, the success rate of ERC was 70% (14/20 patients). This was much higher than the success rate in biliary stricture within 3 months. In type 3, the splint had been located at the anastomosis for 3 months (n = 15), on the other hand, in type 4, the splint was dislocated within 3 months (n = 5). The success rate of ERC was higher in type 3 than in type 4 (73.3% versus 60%), but there was no significant difference.

Discussion

In this study, we focused on factors those could influence on success rate of endoscopic intervention for biliary stricture following LDLT. Among the various factors, one of the characteristics of this study was evaluating the effect of intraoperative placement of biliary splint.

The success rate of ERC in our study was 63.6%, which was comparable to previous reports about the success rate of ERC for biliary stricture after LDLT (58.3–77.5%).[1,10,11] In the ERC procedure, it is important to well understand the biliary anatomy of each graft, number of graft bile duct orifices, and the operative procedure with or without ductoplasty. We share the information about the biliary anatomy and the procedure among surgeons and gastroenterologists who are in charge of postoperative endoscopic intervention.

It has been reported that the risk factors in failed ERC are recipient age, operative time, and morphology of the stricture.[28] In this study, no significant risk factors were recognized in pretransplant, intraoperative, and posttransplant factors.

Liu *et al*[8] reported that the biliary splint itself caused cholangitis or fibrosis and led to biliary stricture.[8] When we retrospectively studied the duration of biliary splint placement among 148 adult LDLT recipients between April 2005 and July 2015, the splint was dislocated within 3 months in 26.7% of recipients, whereas it had remained in place for 3 months in 73.3% of recipients. The incidence of biliary stricture was equal regardless of the duration of splint placement. Although we have not compared the patients with or without biliary splint, a relationship between biliary splint placement and fibrosis of bile duct based on the results of this study were not evident.

We divided biliary strictures into early strictures that occurred within 3 months after LDLT, and late strictures that occurred later than 3 months after LDLT. In this study, only 2 cases developed early strictures. In these 2 cases, the splint was dislocated before the diagnosis of stricture (type 2). Furthermore, ERC intervention failed in these 2 cases; hence, the success rate of ERC in early biliary stricture was 0%. Whereas, no cases developed an early stricture in recipients with planned splint placement until 3months after transplant (type 1).

The pathogenesis of biliary strictures might differ between early stricture and late stricture. We surmise that severe anastomotic fibrosis was induced in early stricture accompanied with dislocation of biliary splint; as a result, it resulted in unsuccessful cannulation to the anastomotic stricture. In this study, we defined 2 types of late stricture. One was biliary stricture with splint placement for 3 months (type 3) and another was stricture with spontaneous splint dislocation before planned timing of removal (type 4). The success rates of ERC in type 3 (73.3%) or type 4 (60%) were

much higher than the success rate in the cases with early stricture (0%). There was no significant difference in the success rates of ERC between type 3 and type 4. Therefore, we concluded that intervention under ERC was highly effective approach for late biliary stricture regardless of the duration of splint placement.

Given the results of this study, early biliary stricture did not occur in patients who kept placing a biliary splint for 3 months. Therefore, to avoid early stricture by biliary splint was considered to be associated with successful endoscopic intervention for biliary stricture. By placing a biliary splint, we can ensure the patency of the biliary anastomosis and prevent the incidence of early stricture.

In this study, the splint was dislocated in 31.8% of recipients. To prevent dislocation, we need to evaluate the methods for fixing the splint and the location of the splint tip. In addition, in case of splint dislocation, we must recognize that endoscopic treatment for biliary stricture may be difficult; therefore, we need to carefully follow such patients not to avoid appropriate timing of endoscopic intervention for possible biliary stricture.

There are potential limitations in this study. The study design was retrospective with a small number of patients. Thus, further study with larger samples is needed to confirm our results.

In conclusion, although biliary anastomotic stricture after LDLT is a complication that can affect a prognosis, the prevention of early biliary stricture by placing a biliary splint may lead to an improved success rate of endoscopic intervention.

Acknowledgments

Conflict of interest statement: Okada Satomi and other co-authors have no conflict of interest.

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