Biliary Complications Following Orthotopic Liver Transplantation: the Place of Surgical Reconstruction in the Minimally-Invasive Era

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ABSTRACT

Background: Biliary complications are the more frequent problem following liver transplantation (LT) and have been considered the “Achilles’s heel” of this procedure. The aim of this study was to evaluate the rates of biliary complications after LT, the different therapeutic modalities currently available and their outcomes.

Methods: A total of 420 LTs performed up to 2020 were retrospectively analyzed. Evaluation factors included MELD score, images, surgical techniques, type of biliary reconstruction and type of complications. We also analyzed the different therapeutic options, and the short and long-term outcome.

Results: 417 deceased donors and 3 living donor transplants were performed. Biliary complications occurred in 37 patients (8,8%) – 31 strictures (81%), four leaks (11%), one acute biliary peritonitis after T-tube removal (3%) and two patients biliary stones (5%). Biliary complications associated with vascular complications were seen in 10 patients (27%). In general, a minimally invasive management (percutaneous or endoscopic) was the first-line approach. Percutaneous interventional procedures were the treatment of choice in 32/37 patients (86,48%), with a success rate of 67.74% (21/31). Hepaticojejunostomy (HJ) was performed in 14 patients. Overall morbidity rate of surgical reconstruction was 14% (2/14 patients) and perioperative mortality was 7%. The median follow-up was 54,53 months. At follow-up, none of the patients in the HJ group had developed a new stricture.

Conclusions: The majority of biliary complications must be treated by minimally invasive approach. However, when those fail, surgical reconstruction allows to avoid future consequences in the graft.

Key words: biliary complications, orthotopic liver transplantation, biliary strictures, biliary leaks

INTRODUCTION

Liver transplantation (LT) is currently the standard therapeutic procedure both for patients with end-stage liver disease and with acute liver failure. Surgical techniques, immunosuppression, and postoperative management have steadily improved resulting in better patient outcomes. However, complications involving the biliary tract continue to be a frequent problem after transplanta-

Received: 30.12.2020

Accepted: 27.02.2021

tion. The most common biliary complications (BC) are biliary strictures (BS) and biliary leaks (BL), and the estimated incidence ranges between 6 to 35% (1,2,3,4). These complications often result in surgical reinterventions, hospital readmissions, higher costs, and contribute to significant morbidity and mortality rates. These complications are seen both in deceased donor liver transplant (DDLT) and living donor liver transplant (LDLT), although they are more frequent in the latter (2,5,6,7). Treatment modalities will depend on the type and severity of the complication, and the type of biliary reconstruction used at the time of the LT, Duct to Duct anastomosis (D-D) or hepaticojejunostomy (HJ) (8). Minimally invasive (MI) treatment of BC with an endoscopic or a percutaneous approach has become a mainstay in the management of post-transplantation BC (9), leaving the surgical intervention for a small proportion of patients in whom the MI approach has failed. The success rate of the endoscopic approach reaches 80% in experienced hands (9,10). If unsuccessful with endoscopy (11), percutaneous transhepatic management can be a good alternative therapy (12). Early identification and adequate treatment of recognized BC following LT are fundamental in reducing the morbidity and mortality rates of this complication and ensuring graft and patient survival. The decision on which technique has to be employed therefore depends on the type of BC and the experience in endoscopic or percutaneous approach, leaving surgical revision as the last option (12). The focus of this review will be the discussion on the types, diagnosis, and results of different treatment modalities for BC following LT and the current place of surgical reconstruction.

MATERIAL AND METHODS

In this study, we retrospectively reviewed the records of 420 liver transplantation in two different Centers, until 2020. The first period (1996-2004) at the Italian Hospital of Cordoba with 45 patients, and the second period at the Sanatorio Allende of Cordoba with 385 patients between 2005 and 2020.

The Child-Pugh model and waiting time for liver graft allocation was used until 2005; afterwards the MELD score was used.

Patients follow-up was held in the transplant outpatients office at least once per month, and comprised physical examination, blood chemistry and images (US-TC-RM) when necessary.

The surgical technique employed for cadaveric and

LDLT was described by Starzl in 1963 (13,14,15,16).

Venovenous bypass with pump and T-tube insertion was used only in the first 35 recipients. Since 2005, all procedures were performed with Piggy-Back Technique. The biliary reconstruction was usually performed as an end-to-end anastomosis between the donor common bile duct and the recipient common hepatic duct with interrupted or running 6-0 monofilament absorbable suture, polydioxanone (PDS; Ethicon, Somerville, NJ). When the indication for LT was a biliary disease (such as primary sclerosing cholangitis), when there was a marked discrepancy between the bile duct sizes, and during re-LT, we preferred to perform a Roux-en-Y HJ. Two to three closed-suction abdominal drains were routinely inserted.

Medical records of all patients who underwent liver transplantation were reviewed. The analyzed data included, age, sex, co-morbidity, indication of liver transplantation, cold and warm ischemia time, type of biliary complication and treatment modality used.

We defined BC as strictures, leaks, or the presence of common bile duct stones. Furthermore, complication after T-tube removal was also considered as biliary complication. Anastomotic biliary strictures or bile duct stones were suspected in the presence of elevated serum bilirubin and/or alkaline phosphatase levels and confirmed by ultrasonography (US) or magnetic resonance (MR) cholangiography findings. Anastomotic bile leaks were diagnosed by the presence of bile in the abdominal drains, radiologic evidence of a leak, or the presence of an intra-abdominal biloma. T-tube related complications occurring after removal, developing biliary peritonitis. When a BC was diagnosed on the basis of clinical suspicion (jaundice, pruritus), increased ALP, gGT and hyperbilirubinemia, biliary duct dilatation or stenosis at ultrasound and confirmed by MR imaging, we considered patients for an initial MI percutaneous or endoscopic approach, depending on the type of complication. The surgical revision was considered after failure of MI techniques or according to the type of complication.

Follow-up for non surgical therapy was 21 months (1 to 111) and for surgical approach was 54,53 months.

All quantitative data are expressed as median (range). Qualitative data are expressed as numbers (%). The Mann-Whitney U test for continuous variables and Pearson's chi-square test were used when applicable, or Fisher's exact test for categorical variables. Statistical analyses were performed using SPSS 20.0 (SPSS Inc, Chicago, IL, United States). A p-value of less than 0.05 was considered statistically significant.

RESULTS

Patient demographics of the study group and primary liver disease of patients undergoing LT are presented in *table 1*. Etiology of LT in patients with biliary complication are listed in *table 2*.

Of the total cohort, duct-to-duct (D-D) biliary anastomosis was performed in 379 transplants (90%), whereas a Roux-en-Y HJ was done in 41 patients because of primary disease of the bile ducts (sclerosing cholangitis or primary biliary cirrhosis), or due to biliary duct disparity.

The mean age of recipients in the entire cohort was 38 years old (range 6 to 71).

Mean age of the BC group was 55 years (range 16 to 70 years). A total of 19 (54,28%) were males and 16 females.

University of Wisconsin (UW) preservation solution was used in 372 (88,58%) cases and HTK in 48 (11,42%); 28 patients in whom UW solution was used presented a BC whereas 9 out of 48 (18,75%) patients in the HTK solution group were associated with this complication ($p=0.02$).

Three hundred and eighty-five patients (91,66 %) were listed according to the MELD score on an average value of 27 (range 21-30). Mean Meld score in complicated patients was 30 (range 23-38) (NS).

Mean cold ischemia time (CIT) in the BC group was 7,42 hours, and warm ischemia time (WIT) 35 minutes, without significant differences with the control group. In the BC group, five out of 37 had more than 9 hs of CIT and 32 out of 37 had less than 8hs.

Thirty-seven patients presented some type of BC, with an overall rate of 8.8%. Thirty-one patients presented with a BS (81%), six with anastomotic leaks (AL), out of which four were associated with biloma and two ultimately developed a BS; one patient suffered from an acute biliary peritonitis after T-tube removal and two patients had common bile duct lithiasis, one of them in the context of a BS. None of them was associated with HCC.

Biliary complication associated with vascular complication was seen in 10 out of 37 (27%).

The mean time between LT and the occurrence of a BC was 130 days for BS and 60 days for AL (*table 3*).

Management overview of BC patients is presented in *fig. 1*.

The initial management of patients with BC was a percutaneous approach in 32 (86,46%) recipients. A Rome Protocol was indicated in three of these patients (9.37%) because of failure of primary percutaneous dilatation.

Table 1 - Indications in 420 Liver Transplantations - HCC was associated in 19 patients

Etiology	Total/plus HCC		%
alcoholic	110	5	26,19%
autoimmune	79	1	18,80%
HCV	47	6	11,19%
Criptogenetic	44		10,57%
NASH	27	4	6,47%
FHF	27		6,47%
PBC	26		6,19%
Haemochromatosis	26	3	6,19%
Cr. Rejection	9		2,14%
SBC	6		1,42%
EC	6		1,42%
HBV	5		1,19%
H. Art.Trom	2		0,47%
Budd Chiari	2		0,47%
Caroli	2		0,47%
hemangioendothelioma	1		0,23%

Table 2 - Etiology of liver transplantation in patients with biliary complication. None of them had HCC

Etiology	Total	%
autoimmune	9	5,71%
alcoholic	7	20%
Hemochromatosis	3	8,57%
Criptogenen	3	8,57%
PBC	3	8,57%
NASH	3	8,57%
VHC	3	8,57%
2 CB	3	8,57%
Fulminant	1	2,85%

Table 3 - Summary of patient characteristics

	Complicated	Not Complicated
Age/year	55 (16 - 70)	38 (6 - 71)
Sex	F/M 147/236	F/ M 17/20
Meld Score	30 (23 - 38)	27 (21 - 30)
Preservation Solution	UW/HTK 28/9	UW/HTK 344/39
Cold Ischemia Time	7 hs 42' (2hs 46' - 10 hs 40')	7 hs 50' (5hs 50'-10hs 55')
Warm Ischemia Time	35' (18-56)	33' (19-35)

The standard MI approach consisted of an initial percutaneous transhepatic drainage (PTD) followed by sequential balloon dilatations as required. In general, two to four procedures were needed, with an average of two dilatations per patient. There was no morbidity in the PTD group but one patient died as consequence of a duodenal perforation after the procedure.

The percutaneous management was successful in

Figure 1 - Management overview of biliary complications after LT.

Abbreviations: BS, biliary stricture; CBD, common bile duct; PTD, percutaneous transhepatic drainage; ERCD, endoscopic drainage; HJ, hepaticojejunostomy.

22 of the 32 patients (68,7%). Mean follow-up was 21 months (1 to 111).

Endoscopic treatment was performed in one patient. The indication for this approach was a non-anastomotic stricture associated with cholangitis. This patient eventually underwent an HJ because of persistence of the stricture.

One patient who presented with biliary peritonitis after T-tube removal only required an exploratory laparotomy and drainage of the abdominal cavity.

In total, 14 of 37 (38%) patients underwent an HJ. Ten patients in whom the PTD had failed, one for failure of the endoscopic approach, and as initial treatment in three patients, who presented with CBD stones and BS (5,4%). The morbidity rate after surgical revision was 14% (2/14); one of these patients presented an anastomotic leak and the second one presented an intrahepatic infected hematoma requiring percuta-

neous drainage. one patient died after the procedure due to septic complications (mortality rate of 7%). Median follow-up of HJ was 54,53 months (range 1 to 120 months). At follow-up, none of the patients in the HJ group had developed a new stricture.

No patient needed a re-transplantation because of therapeutic failure of the involved techniques.

DISCUSSION

Complications involving the biliary tract remain a common problem following orthotopic LT and can potentially lead to graft failure with significant morbidity and mortality rates.

Out of 420 LT performed in the study period, 37 (8,80 %) suffered from a BC during follow up. In the reported literature, the incidence of this complication ranges from 6% to 35% (1,2,3,4). We believe that

our low incidence regarding BC is the small number of LDLT as well as split liver procedures, which are known risk factors for developing this complication (6,17,18,19,29,39).

There were no differences in the MELD score between patients with and without biliary complication (20). But when we compare before and after MELD score adoption, we observed that the rate of biliary complications has increased with the adoption of the MELD (21).

Regarding CIT and WIT, we do not have significant differences between complicated patients and those without complication. In previous reports, only a WIT > 49 minutes has been associated with AL (22), and the mean WIT of our cohort was 35 minutes, which can explain why there were no differences.

Foley et al and Axelrod et al. described donation after Cardiac Death Donors as a risk factor for BC, but this is not still regulated in our country (21,23,24).

We preferred D-D biliary anastomosis except when the indication of LT was biliary disease. The non-traumatic, running or interrupted suture, with monofilament absorbable material is the technique of choice for end-to-end ductal anastomosis (32). However Esfeh et al. report comparable outcomes between D-D and HJ in selected PSC patients (25). Kaldas et al. reported in 2019 that non absorbable suture is an independent risk factor to BC (26).

Around 70% of BC occurs in the first year after LT (27); however it may appear up to several years after transplantation. In our study, the median time from LT to the occurrence of BL was 60 days (15-120) and 130 (30-400) days for BS.

BS were the predominant complication in 31 of 37 patients (81%); four patients had simultaneous BL and biloma, and two had BL and stricture. One patient presented acute biliary peritonitis after T tube removal for that reason T-tube was assessed as a risk factor, and its use has been rejected.

BS can be presented as Anastomotic strictures (AS) that account for 80% of all strictures, and Non anastomotic strictures (NAS) represented by 20% (28,29).

AS are more prevalent with Roux-en-Y HJ, and are more commonly seen after LDLT than DDLT, because the anastomoses in living donor recipients are made between multiple small bile ducts (30). Usually, they occur in the first 12 months, they tend to be short and localized to the anastomotic site, opposite to NAS that typically occur in multiple sites and are longer in length (31). Pathophysiological factors can be local tissue ischemia, localized edema and fibrosis at the site of the biliary anastomosis (5).

NAS are strongly associated with hepatic artery thrombosis, ischemic damage to the duct or because of immunological factors (32,33). NAS can occur in both the extra- or intrahepatic ducts and average time to development is usually 3 to 6 month (32,34,36).

The biliary tree is supplied solely by the peribiliary vascular plexus which arises from the hepatic artery, through a network of arterioles and capillaries known as the peribiliary vascular plexus. Those vessels are usually ligated during OLT; for these reasons NAS can be attributed to ischemic phenomena (37). Others researchers also found that periductal vascular injury may be a cause of complication (5,38). In our study, the association with vascular problems was 27%.

The diagnosis of biliary complication after LT may be achieved through the use of a variety of imaging modalities, including ultrasound (US), magnetic resonance imaging (MRI), endoscopic retrograde cholangiography (ERC) or percutaneous transhepatic cholangiography (PTC) (5,39,40). We have used preferably US as the first study because of its availability, low cost as well as the valuable information about liver vasculature with US-Doppler. Several reviews of the use of contrast-enhanced ultrasound (CEUS) in liver transplantation have been published. On CEUS, the intra and extrahepatic bile duct can be seen as radiographic cholangiography. CEUS appears to be a good test for the visualization of the bile ducts of liver grafts (41). MRI with cholangiopancreatography is used when we suspect biliary complication after US. Furthermore, MRI provides cross-sectional imaging of the liver and intra-abdominal structures, allowing the detection of a variety of postoperative problems. MRI with cholangiography is the most effective non-invasive imaging modality for the assessment of BC after LT, with a sensitivity and specificity for the diagnosis $\geq 90\%$ (28,35,42). Treatment strategies for BC are based on the type and severity of the complication and the biliary reconstruction technique applied at the time of LT. A MI management, PTC or ERC, is currently the first-line approach (1,4,34,43). These procedures should be considered complementary techniques, and success can be achieved in 70%-90% (1). However, some researchers reported that up to 50% of patients may present new strictures after MI treatment (44). Choo et al. found that acute pancreatitis (21%) and stent blockage (30%) were the main complications after ERC (38). Percutaneous transhepatic management can be used successfully and may be performed to avoid further complications and additional surgical procedures (3,6,45), also in pediatric patients (45).

Biliary leaks can be treated conservatively by main-

taining the abdominal drain if the patient's condition is stable. Cut surface leaks or small caudate duct leaks usually respond to the conservative approach and resolve in 5-8 weeks. Anastomotic leaks, however, require additional intervention. Patients with duct to duct anastomosis can be treated successfully with percutaneous approach (2,20) or with ERC, with reported success rates of 80%-90% (28). Whereas small leaks can be managed by endoscopic sphincterotomy alone, management of significant anastomotic bile leaks may require stent placement with a success rate of approximately 50% (32). The remainder of cases require surgical revision, especially in early leaks or when the patients are unstable. Bilomas are usually treated by insertion of a percutaneous catheter with high rates of success (32,34).

Second line treatment is PTD. This technique is generally performed when ERC is not feasible, because of a Roux-en-Y biliary enteric anastomosis, or when ERC has failed because of complex or tight strictures. Bile duct stone complications, especially after HJ are treated by a percutaneous approach (46) although Tsutsumi et al. report the success with both PTD and endoscopic procedures (20). Also, multiple endoscopic plastic stents are currently used in patients with BS of D-D anastomosis but are associated with an increased rate of pancreatitis (32,47).

Although PTD has an overall technical success rate of 40% to 85%, it remains a second-line therapy because of its potential complications, such as hemorrhage, bile leaks, and infection (2%-14%) (47,48).

The risks of hemorrhage from PTD may be particularly problematic in patients with persistent thrombocytopenia or coagulopathy after transplant. Furthermore, there exists more discomfort for patients undergoing PTD due to the presence of an external catheter throughout a course of treatment that can extend over many months. Despite the aforementioned, we prefer this method because we have achieved great expertise with it with a success rate of 68,7%.

Surgical revision is now reserved for patients who have strictures refractory to either ERC or PTD and in whom retransplant is the last resort after all other treatment modalities have failed (4,32).

When surgical revision is required for patients with a D-D anastomosis, the most commonly performed procedure is a Roux-en-Y HJ. If an HJ was performed initially because of PSC or another bile duct abnormality, then an attempt is made to reposition the bile duct graft to a better vascularized area (49). We performed 14 HJ in 37 BC (38%). In 11 patients due to failure of MI treat-

ment; 14% of this group presented some complication, and one patient (7%) died. Davidson et al. (12) reported an overall morbidity rate of 26% after revision HJ and a mortality rate of 6.5% which is in line with our own findings. The success rate in terms of anastomosis patency was 100%, with a follow-up of more than 54 months. HJ has demonstrated to be a safe and effective procedure with short hospital stay and fast recovery (12,16,17,50).

Even though the success rate with HJ is superior to MI techniques in terms of anastomosis patency, we think that the initial approach with a percutaneous treatment is justified given that our success rate with this technique is around 70%, added to the known benefits of this approach, such as shorter length of stay, faster recovery and lower costs.

CONCLUSION

Biliary complications remain a frequent problem after LT and there are currently multiple treatment modalities. BS is the more common complication. Early recognition and adequate treatment are pivotal to reducing morbidity and mortality, improving patient and graft survival. MI management of these complications is the best initial approach; in our experience, PTD followed by balloon dilatation for BS is a very good alternative, with low complications rate and good long term results, but when these procedures fail, we recommend the surgical intervention to ensure the viability of the graft.

Author contributions

All authors contributed equally to these work.

Conflict of interest

There are no conflict of interest to disclose.

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