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Journal of Nanjing Medical University, 2009, 23(2):87-92
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Review

Biliary complications in orthotopic liver transplantation: mechanism, diagnosis and treatment

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Received 12 November 2008

Abstract

Biliary complications(BC) are a major cause of morbidity in liver transplant recipients with an incidence of 10~30% following orthotopic liver transplantation(OLT), and a mortality rate of up to 10%. The most common biliary complications are bile leaks, biliary strictures, ampullary dysfunction, and stones. Leaks predominate in the early posttransplant period; while stricture formation typically develops gradually over time. Risk factors for biliary complications comprise technical failure, T-tube-related complications, hepatic artery thrombosis, bleeding, ischemia/reperfusion injury, primary diseases, and other immunological, non-immunological, and infectious complications. Cholangiography, such as endoscopic retrograde cholangiopancreatography(ERCP) or percutaneous transhepatic cholangiogram(PTC), is considered the gold standard for identifying post-transplant BC. The management of biliary complications after OLT requires a multidisciplinary approach, in which interventional radiology and endoscopic techniques are emerging as the preferred treatment option, but in a selected majority of patients, surgery is still necessary.

Keywords: liver transplantation; bile-duct complication; ischemic-type biliary lesions.

INTRODUCTION

Since the first performance in 1963, orthotopic liver transplantation(OLT) has evolved into the optimum treatment for end-stage liver disease, with 1-year survival rates of 90% and a 10-year predicted survival of 70%[1]. Improved survival has been achieved by better organ selection, retrieval, preservation and immunosuppression, as well as changes in surgical technique and postoperative care. However, biliary complications(BC), once considered as the technical "Achilles heel" of OLT, still remain a common source of morbidity and mortality. They result in morbidity rates of 10%~30% and mortality of 10%[2]. The most common biliary complications are bile leaks, biliary strictures, stones, and ampullary dysfunction. Leaks predominate in the early post-transplant period; stricture formation typically develops gradually over time. Approximately one-third of biliary complications occur within 1 month of surgery, and 80% within 6 months[3]. In this article, the risk factors for the development of biliary complications, their etiology, their diagnosis, and their treatment will be reviewed in brief.

RISK FACTORS FOR BILIARY COMPLICATIONS AFTER OLT

Technical factors

Biliary Reconstruction

There is no consensus on optimal biliary reconstruction, and considerable variability exists between transplant centers. The choice may be influenced by multiple factors, such as underlying liver disease, size of donor and recipient bile ducts, and prior transplant or other biliary surgery. The critical aspects of performing the biliary anastomosis, as in most other gastrointestinal surgery, include ensuring that the tissues have adequate blood supply, are free of tension, and can be approximated with minimal mechanical trauma. Options for biliary reconstruction include creating an anastomosis between donor and recipient

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bile ducts(choledochocholedochostomy) and creating an anastomosis between donor bile duct and recipient jejunum (choledochojejunostomy).

A choledochocholedochostomy(CC), which may be performed end-to-end or side-to-side, is the procedure of choice in most centers following whole organ OLT in patients with healthy native bile ducts of suitable caliber. There are certain advantages of CC, such as the incorporation of the well vascularized recipient common bile duct, decreasing the risk of ischemic-type biliary lesions(ITBL), and the preservation of the sphincter of Oddi, which prevents the reflux of enteric contents into the biliary tree, thus potentially decreasing the risk of ascending cholangitis[4]. A choledochojejunostomy(CJ) with a Roux-en-Y loop is utilized in cases of primary biliary tract disease (sclerosing cholangitis, biliary atresia), large disparity in size or small caliber ducts, and may be preferred in cases of retransplantations because of inadequate recipient duct length. The most common causes of early bile leaks and anastomotic strictures are related to imperfect surgical techniques during the course of biliary reconstruction, such as suture-related insufficiencies or stenoses, and vascular factors.

T-tube related complications

There is ongoing discussion regarding the use of a T tube for duct-to-duct anastomosis in liver transplantation. A T-tube drainage at OLT has traditionally been used to provide easy access to the biliary tree and lower the pressure in the biliary system, which may be elevated in the case of stenosis at the anastomotic site, or due to sphincter of Oddi dysfunction. Additionally it aids monitoring of the quality and output of bile and may reduce the incidence of late anastomotic biliary strictures[5], and the need for their surgical repair[6]. Biliary drains, however, may increase complication rates by frequently observed leaks following bile drain removal, its dislodgement, cholangitis and biliary obstruction[5]. The incidence of biliary drain-related biliary complications range between 10% and 22%, with bile leak after bile drain removal occurring in 5%~15% of patients[5,7]. This is due to inadequate development of a fibrous fistulous tract along the course of the drain as a result of impaired fibrogenesis from immunosuppression with the use of steroids. Several measures have been proposed to reduce the incidence of biliary leaks following bile drain removal. These include the use of rubber tubes instead of silicone ones, leaving a counter drain or the T-tube in the tract under fluoroscopic guidance[8], or delayed removal of biliary drains until 4~6 months after OLT[9]. Transcystic or internal endobiliary stents, as well as routine interventional radiologic procedures have also been proposed to overcome these problems[2,9,10]. Many groups have abandoned the use of a T tube with whole-organ OLT, and this has been shown to be safe, efficacious, and cost-effective, compared to biliary reconstruction using a T-tube[11]. This practice conforms with the results from two prospective, randomized trials showing no advantage of biliary drainage in whole-organ OLT[5]. According to some authors, and our own experience, biliary decompression of duct-to-duct anastomosis may be more indicated in partial-liver graft transplantation where it may reduce the risk of both cut surface and anastomotic biliary leaks[12]. However, this has not been confirmed in a prospective randomized study.

Damage to the vascular supply of the biliary tree

The hepatic arterial system is the most important vascular supply for extra- and intrahepatic biliary duct, as well as the ductal anastomosis. Any reason impacting the blood supply from the hepatic artery will cause ischemic-type biliary lesions(ITBL). Many technical factors may be involved, including excess dissection of periductal tissue during organ procurement, the excessive use of electrocautery for biliary duct bleeding control in both donor and recipient, and excess tension on the ductal anastomosis[13].

Acute hepatic artery thrombosis(HAT) is one of the most fatal complications occurring after OLT and should be ruled out in any type of biliary complication. The incidence of HAT was reported to be approximately 3%. Some 50% of patients who present with nonanastomotic strictures have HAT. HAT can easily result in serious ITBLs, and then bile leaks, biliary strictures and hepatic abscesses may take place, with a mortality up to 35%~50%[14]. Stange *et al.*[15] reported 30 cases of HAT, among which over a half had complicated cholangitis, ischemic-type biliary necrosis, and 14 cases required retransplantation.

Non-technical factors

Ischemia-Reperfusion injury

Nonanastomotic intrahepatic strictures(NAS) are considered to be the most troublesome biliary complication. NAS were first described in OLT associated with hepatic artery thrombosis, where the biliary tree becomes ischemic and eventually necrotic, resulting in a typical cholangiographic picture of biliary strictures, dilatations, and intraductal cast formation. However, these cholangiographic abnormalities of strictures and dilatations can also be seen in patients who do not have hepatic artery thrombosis. So the term "ischemic-type" biliary lesions(ITBL) has emerged.

Cold ischemic injury

An increased frequency of such lesions in patients was noticed with prolonged cold ischemia time[16],

delayed rearterialization of the graft, or transplants from non-heart-beating donors[17], suggesting ischemia-reperfusion injury as a causative factor. The injury can be explained by either direct ischemic damage of the biliary epithelium; increased susceptibility of the biliary epithelium to a second factor, such as reoxygenation injury; or secondary ischemia of the biliary epithelium due to damage to the peribiliary arterial plexus[16]. Sanchez-Urdazpal et al[16] reported an incidence of ITBL of 2% in livers with a cold ischemia time(CIT) of less than 11.5 h, rising to 35% in livers with a CIT between 11.5 h and less than 13 h, and even up to 52% in grafts with a CIT of more than 13h. Nowadays many centers therefore try to keep the CIT below 10 h. In addition, it has been suggested that bile salts within the biliary tree can be cytotoxic to the ductal epithelium of grafts with long cold preservation times, resulting in intrahepatic stricture formation[17]. For this reason most surgeons routinely flush the donor biliary tree to remove stagnant bile at the time of organ procurement in order to prevent direct chemical injury of the biliary epithelium by bile during cold storage. Pressurized aortic perfusion, as well as the use of low viscosity preservation solutions, have also been proposed as additional important measures that may limit the incidence of biliary strictures in the liver transplant setting[18].

Warm ischemic injury

Two periods of warm ischemia can be distinguished during the transplant procedure. The first warm ischemia time(WIT), during harvesting and before cold preservation, and the second WIT, during graft implantation and before complete reperfusion. The first WIT, especially, is a major concern in grafts from non-heart-beating(NHB) donors.

Several studies have shown that liver grafts from NHB donors are at increased risk of developing ITBL[19-20]. Concern exists that increased harvesting time, extending the first WIT, in addition to subsequent CIT and ischemia-reperfusion injury, may result in damage to the biliary epithelium[19].

To reduce the incidence of ITBL, attempts have been made to reduce the second WIT. During revascularization of the graft, the most common technique is initial reperfusion via the portal vein, with subsequent reconstruction and reperfusion of the hepatic artery. Bile ducts, solely dependent on the hepatic artery for their blood supply, are exposed to warm ischemia during reperfusion via the portal vein alone. This situation has been hypothesized to increase damage of the biliary epithelium. To overcome this potentially harmful situation, Sankary *et al.*[21] have studied the impact of simultaneous versus sequential reperfusion of the portal vein and hepatic artery on the incidence of ITBL. These investigators observed a significant reduction of ITBL when livers were reperfused simultaneously via the portal vein and hepatic artery. However, in a more recent study, we were not able to demonstrate a favorable effect of simultaneous arterial and portal reperfusion on the incidence of ITBL[22].

Immunosuppressants

Immunosuppressants are routinely used to control immunological rejection after OLT, but they also impair the body's resistance and bacterial/viral(especially CMV) infection may occur, increasing the morbidity of BC. Anti-proliferative immunosuppressants such as rapamycin and mycophenolate mofetil, may further increase the incidence of biliary complications by impairing wound healing.

Other factors

ABO blood-type incompatible

ABO blood type-mismatched liver transplantation has long been recognized to give rise to multiple complications. The incidence of BC in ABO- incompatible OLT varies from 20% to 82%[23]. An explanation for this could be the fact that the antigens of the blood-type system are not only expressed on the vascular endothelium but also on biliary epithelial cells, making them a target for preformed ABO blood group antibodies[23]. Because of the high rate of complications and reduced graft survival rates, transplantation across the ABO border is discouraged. However with the usage of plasmapheresis before OLT and more effective immunosuppressants, ABO incompatible transplantations are no longer an absolute contraindication to OLT. Actually, recent reports suggest that with sufficient pre-operative preparation, the 5-year survival rates of ABO incompatible transplantations is similar to that of the classic procedure[24].

Cytomegaloviral(CMV) infections

The morbidity of CMV infections reaches 30-65% after OLT. Halme *et al.*[25] surveyed 100 follow-up cases after OLT, and 24 of them developed BC, among which 18 cases were serum CMV-Ag(+). Furthermore, CMV infections have been proven to be related to chronic rejections which might result in vanishing bile duct syndrome(VBDS). Arnold *et al.*[26] reported 12 cases of VBDS, of which 10 cases presented as CMV-DNA(+). Primary hepatic diseases(PSC)

It has been well described in several studies that patients who are transplanted for PSC have a higher incidence of ITBL after transplantation[27,28], and the recurrence rate of PSC is as high as 37% according to recent research[29]. The association between ITBL and AIH has only been described recently[27]. PSC and AIH

share a similar genetic predisposition to autoimmunity[27]. Taken together, these findings strengthen the hypothesis that ITBL may have an underlying(auto) immune component.

Chemokines

Chemokines play a key role in postoperative immunomodulation, especially during rejection, as well as in postischemic injury. Evidence for a role of chemokines in the pathogenesis of ITBL after OLT has been provided by a genetic association study focusing on CC-chemokine receptor 5(CCR5). CCR5 is a receptor for CC-chemokine ligand(CCL) 3(macrophage inflammatory protein 1 alpha) and CCL4(macrophage inflammatory protein 1 beta), which are over-expressed in infiltrating leukocytes[30]. Biliary epithelial cells have been shown to produce CC-chemokines that may bind specifically to CCR5. CCR5Δ32 polymorphism is a nonfunctional mutant allele of CCR5, with an internal deletion of 32 base pair. Recently Moench *et al.*[31] found a very strong association between the presence of the CCR5 Δ32 polymorphism in recipients and the development of ITBL after OLT. These findings add to the existing evidence that immunological factors play a role in the pathogenesis of ITBL.

CLINICAL PRESENTATION AND DIAGNOSIS OF BC

Patients with biliary complications may present with a variety of nonspecific complaints, such as right upper-quadrant abdominal pain, fever, anorexia, malaise, abdominal distension, and right-shoulder pain. Jaundice, acholic stools, and bilious ascites are usually late signs. Biochemical indicators such as AST/ALT, TB/DB and γ-GT may rise, but they are easily obscured by rejections or infections. Imaging examination plays a significant role in the diagnosis of BC[32]. Cholangiography, including ERCP, PTC, MRCP, and cholangiography through a T-tube, is considered the gold standard for identifying post-transplant BC. MRCP has been shown to be a promising noninvasive diagnostic tool for the detection of biliary complications after OLT, especially in patients with bilioenteric anastomosis where the biliary tract is inaccessible by ERCP[32]. In addition, a hepatic biopsy provides satisfactory sensitivity and specificity, so a liver biopsy can be performed in many patients with abnormal biochemical markers prior to cholangiography to exclude rejection and ischemia.

TREATMENT OF BC

Bile leaks

Leakages may be localized at the anastomosis where it is primarily caused by a technically unsatisfactory anastomosis, or ischemic necrosis at the end of the bile duct. Nonanastomotic leaks mainly originate from the T-tube exit site. Nonanastomotic, non-T-tube-related leaks often result from vascular insufficiency, due to HAT or other causes of compromised arterial perfusion. Anastomotic leakages can be successfully managed without surgery if they are small and localized. Biliary tract stenting, with or without endoscopic sphincterotomy, as well as percutaneous treatment, can be applied successfully in over 90% of biliary tract leaks, but subsequent anastomotic strictures occasionally develop[33]. Nonanastomotic leakages are preferably treated by ERCP or PTC with stenting of the bile leak, using plastic internal stents[14,34]. Surgical therapy is the definitive treatment that may be necessary for massive bile leaks if conservative treatment fails, or if there is evidence of HAT. T-tube-related leaks are less likely to endanger the graft or patient and are usually treated conservatively.

Biliary strictures

Biliary strictures are classified as anastomotic and nonanastomotic in site. They may be due to technical causes, ischemia of the biliary tree due to hepatic artery thrombosis or stenosis, or fall into the category of ITBL. Anastomotic strictures can be treated by dilation and stenting of strictures through endoscopic measures such as ERCP, PTC, with a success rate of 75%, while the same means is far less effective in nonanastomotic strictures, achieving a success rate of only 28.6%[35]. If non-operative techniques are unsuccessful, surgery may be appropriate in selected patients. Especially when lesions are predominantly present at the level of the bile duct bifurcation, resection of the extrahepatic bile ducts and Roux-en-Y hepaticojejunostomy should be considered. The presence of ITBL is associated with a marked decrease in graft survival. Ultimately, up to 50% of patients with ITBL either die or need a retransplantation[24,28].

Other biliary complications

The incidence of ampullary dysfunction is approximately 2%~5% after OLT. Operative denervation of the sphincter of Oddi has been hypothesized to impair ampullary relaxation, causing extrahepatic cholestasis. ERCP shows the typical sign of biliopancreatic reflux of contrast medium. Endoscopic sphincterotomy and/or biliary stenting is usually a successful treatment[36], but a hepaticojejunostomy may occasionally be required. Biliary stones and sludge usually occur later than 3 months after OLT and are mostly associated with biliary strictures. Other factors may be foreign bodies (T-tube, stents), mucosal damage, kinking of the bile duct, infection, and ischemia. Endoscopic sphincterotomy and stone extraction will be effective in most patients[36].

Conversion to Roux-en-Y CJ may be required in those with unextractable stones casts.

CONCLUSION

Despite progress in surgical techniques, immunosuppression, diagnostic methods, and therapeutic strategies, biliary complications still remain an important source of morbidity and mortality after OLT. Emphasis should be put on the prophylaxis, diagnosis, and treatment of BC, so as to reduce its hazard as well as increasing the long-term survival rates of recipients.

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