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# Liver Transplantation: The Last Measure in the Treatment of Bile Duct Injuries

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**Abstract**
*Background* Bile duct injury (BDI) is a severe complication that may arise during the surgical treatment of a benign disease. A significant proportion of cases develop end-stage liver disease and a liver transplant is required. The aim of this study was to analyze the indications and results of liver transplantation as treatment for BDI.
*Methods* Between January 1988 and May 2007, 20 patients with end-stage liver disease secondary to BDI were included on the liver transplant waiting list. Retrospective charts were analyzed and survival was estimated by the Kaplan–Meier test.
*Results* Four patients died while on the waiting list and 16 received a transplant. Injury to the bile duct occurred during a cholecystectomy in 13 of 16 patients, with the main cause of the lesion being duct division in six patients and resection in four. All patients had received some surgical treatment (median = 2 procedures) before being considered for a transplant. The liver transplant came from a cadaveric donor for all patients and the median time between BDI and liver transplant was 60 months. Two patients died in the postoperative period and nine had complications. Three patients died in the late postoperative period. Median follow-up was 62 (range = 24–152) months. One-, three-, and five-year survival rates were 81, 75, and 75%, respectively.
*Conclusion* Complex bile duct injuries and bile duct injuries with previous repair attempts can result in end-stage liver disease. In these cases, liver transplantation provides long-term survival.

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## Introduction

Bile duct injury (BDI) can occur during any surgical procedure performed in the upper abdomen. The relatively higher frequency of the cholecystectomy procedure results in it being the most common procedure that leads to BDI [1]. BDI is associated with a greater risk of perioperative morbidity and mortality, a reduction in the quality of life, and a decrease in long-term survival [2–4]. This is of the utmost importance since, in most cases, injuries occur in young patients undergoing surgery for a benign disease [5].

Given that injuries in a high percentage of patients are initially unsuspected, the postoperative recovery may be prolonged and the possibility of a successful repair reduced [6–8]. Several surgical, endoscopic, and percutaneous procedures may be necessary to manage the lesions and to treat coexisting complications [9]. In spite of these options, a significant percentage of cases develop end-stage liver disease or present with complications that are intractable to common methods of management. Although liver transplantation may constitute the only solution available in these cases, very few articles have been published to address this issue [10–15]. We reported on a series of eight patients who underwent liver transplantation following a BDI [16]. The aim of the present review of this larger group of patients is to analyze the indications and results of liver transplantation as a treatment for BDI.

## Patients and methods

Medical records of hospital admissions and office visits were reviewed retrospectively. Analyzed data included type of initial surgery, mechanism and type of biliary lesion, surgical repair procedures, postoperative outcome, symptoms determining indication for transplantation, time elapsed between occurrence of injury and indication for transplantation, time on the waiting list, transplant features, and subsequent evolution.

The need for transplantation was determined on a multidisciplinary basis and involved HPB surgeons, hepatologists, and infectious disease specialists. Indications for transplantation included one or more of the following: end-stage liver disease with no other alternative treatment and associated with intractable ascites, progressive jaundice, repeated episodes of hemorrhage due to portal hypertension, recurrent episodes of cholangitis, intractable pruritus, and/or poor quality of life [17]. Patients meeting these criteria and with no contraindications for liver transplantation were included in the waiting list. Priority was considered in accordance with the categorical stratification system used in Argentina until the introduction of MELD score in 2006 (Table 1).

A pretransplant workup was carried out in all cases. Multiple diagnostic methods were used to detect the type of BDI and potential associated complications depending on the patient's presentation [ultrasound, computed tomographic (CT) scan, endoscopic retrograde cholangiopancreatography (ERCP), percutaneous transhepatic cholangiography (PTC), magnetic resonance cholangiography, and intraoperative cholangiography]. Arterial damage was suspected from reports of the initial surgery, the mechanism of the BDI, Doppler ultrasound, or CT scan and was finally confirmed by angiography. BDIs were described according to Strasberg's classification [18].

All transplants were performed using whole-liver grafts from cadaveric donors following the standard technique for vascular reconstruction with or without the piggyback technique, depending on the clinical condition of the patient. Biliary reconstruction was undertaken with a Roux-en-Y hepaticojejunostomy using polypropylene 7/0 suture.

A multidisciplinary team was responsible for the postoperative care. All patients received a standardized immunosuppressive regimen (Table 2). Antibiotic and antifungal prophylaxis was administered to all recipients. Postoperative complications were classified according to the criteria proposed by Dindo et al. [19]. Follow-up was carried out until submission of this article or patient death. The Kaplan-Meier test was used for survival analysis.

## Results

Between January 1988 and May 2007, 663 liver transplants were performed at Hospital Italiano de Buenos Aires, Argentina, 449 of which were adult recipients. Of these, 20 patients with BDI as an indication for transplantation were included in this study. Nineteen of these 20 patients were referred from other centers. Four patients (20%) died while on the waiting list due to septic or hemorrhagic complications and 16 underwent transplantation. These 20 patients represent 3.5% of all the liver transplants performed in adult recipients and 7.3% of all the bile duct injuries treated during the same period ($n = 171$).

The 16 liver transplant recipients comprised 8 men and 8 women, with a median age of 45 (range = 26–62) years. The most common surgery during which BDI occurred was cholecystectomy ($n = 13$), while the most frequent mechanisms of injury were bile duct division (6 cases) and resection of the duct (4 cases). The right hepatic artery was injured in four cases, while in one patient the right portal

**Table 1** Categorical stratification system used in Argentina until 2006 to prioritize patients for liver transplantation

| | |
|---|---|
| Emergency | Fulminant hepatic failure or subfulminant hepatic failure with encephalopathy grade III–IV, retransplantation for primary nonfunction or vascular thrombosis with hepatic gangrene |
| Urgency | Fulminant hepatic failure or subfulminant hepatic failure with encephalopathy grade I–II or hepatopulmonary syndrome with $PO_2 < 60$ mmHg or hepatocellular disease meeting two of the following three criteria: creatinine > 1.7 mg/dl, total bilirubin (TB) > 8 mg/dl, prothrombin time (PT) < 35% or chronic cholestatic disease with TB > 20 mg/dl or PT < 60% |
| Elective | |

**Table 2** Inmunosupression regimen

| | Cyclosporin A | Azathioprin | Prednisone | Mycophenolate mofetil | Tacrolimus |
|---|---|---|---|---|---|
| 2 Patients | X | X | X | | |
| 7 Patients | X | | X | X | |
| 5 Patients | | | X | X | X |
| 2 Patients | | | X | | X |

vein was also damaged. According to the Strasberg's classification, lesions included E2 in four patients, E3 in eight patients, and E4 in two patients. This classification was not applied for two patients because one presented with complete stenosis of the biliary duct due to formaldehyde injection, and the other presented with a lesion in the left hepatic duct that occurred during a right hepatectomy. In four cases the lesion was identified during surgery and was repaired immediately. In seven cases it was detected during the first postoperative week and was repaired at the primary center during that stay. In the remaining five patients, the injury was detected in the late postoperative period (due to alteration of hepatic enzymes and cholangitis). All patients except one had undergone previous surgical procedures at the primary center before referral. Table 3 records lesion features, immediate surgical intervention, and other procedures performed.

Thirteen patients were shown to have esophageal varices on endoscopy. A transjugular intrahepatic portosystemic shunt (TIPS) was placed in one patient because of recurrent variceal bleeding nonresponsive to pharmacologic and endoscopic therapy. The main symptoms leading to transplantation were repeated upper gastrointestinal bleeding (9 patients), recurrent episodes of cholangitis (14 patients, with hepatic abscess in 2 cases), intractable pruritus (8), and refractory ascites (7). Patient pretransplantation characteristics are given in Table 4. Median time between lesional surgery and transplantation was 60 months (range = 15–155 months) and median time between the last surgery performed and transplantation was 22 months (range = 1–99 months). The median time on the waiting list was 15 months (range = 1–103 months). During the transplantation procedure, three patients had a patent hepaticojejunostomy confirmed on a HIDA scintigraphy.

Six patients were placed on the waiting list on an elective basis, whereas the remaining ten were considered urgent. Extracorporeal circulation was used in three patients. Median cold ischemia time and operative time were 425 (range = 240–660) min and 465 (range = 240–760) min, respectively. Median red blood cell usage was 4 (range = 0–26) units. Intraoperative injuries included a diaphragmatic laceration requiring pleural drainage and a small bowel perforation requiring local resection, both following division of dense adhesions. No intraoperative mortality occurred. Median intensive care unit and hospital stay were 7 (range = 4–11) days and 20 (range = 11–39) days, respectively. Nine of the 16 patients had postoperative complications (Table 5).

There were no early complications related to the biliary anastomosis. According to Dindo's classification, five complications were grade IIIb and seven were grade II. Two patients died during the postoperative period. One died on postoperative day 7 due to bacterial pneumonia with no abnormality of the graft observed at autopsy. The other deceased patient underwent relaparotomy due to intraperitoneal bleeding. He also required percutaneous drainage of abdominal abscess in the postoperative period and finally died on postoperative day 30 due to sepsis with a normal functional graft.

Three patients died in the late postoperative period. In postoperative month 7 one developed a stenosis of the hepaticojejunostomy that required a revisional anastomosis. During the surgical exposure of the hepatic pedicle, a hepatic arterial thrombosis was evident. Because all the remaining arterial blood supply was compromised, the patient developed fulminant hepatic failure secondary to liver devascularization and required an emergency transplantation. He died on day 4 due to a rupture of a cerebral mycotic aneurysm. The second patient died in postoperative month 17 due to a lung carcinoma with bone metastasis, and the third patient died at 120 months due to an endometrial cancer.

The remaining 11 patients reported good quality of life on follow-up and liver functional tests were within the normal range. Median follow-up was 62 (range = 24–152) months. Survival at 1, 3, and 5 years was 81, 75, and 75%, respectively (Fig. 1).

## Discussion

BDI is considered the most serious surgical complication associated with cholecystectomy [20]. According to different reports, its incidence has remained constant over the years, ranging from 0.1% to 0.9% [21, 22]. With the introduction of laparoscopy, BDI increased to 0.3–1.0%, and at most centers it did not decrease upon completion of the learning curve as would have been expected [23–25]. Moreover, lesions that occur during laparoscopic cholecystectomy result in more serious injury due to the more proximal location of the injury in the biliary tree and the frequent association with vascular injury [18, 26, 27].

Bile duct injuries occur less frequently during surgery for hydatid cysts [10, 28]. In our series, only 2 of the 171 patients (1.16%) treated for bile duct injuries were operated on for this disease. In one case, therapeutic injection of formaldehyde into a hydatid cyst communicated inadvertently with the bile duct and caused complete necrosis of the biliary tree. Hepatic resection surgery, injection of sclerosing agents into the liver, and interventional radiology account for 12% of all BDIs 1. Only 15–33% of bile duct injuries are diagnosed at the moment of the initial surgery [6–8, 20, 26]. In the present series, intraoperative diagnosis was made in 25% of the cases.

The best repair option for patients with complex lesions is a Roux-en-Y hepaticojejunostomy [29, 30]. It is

**Table 3** Characteristics of the lesion

| | Gender | Age | Initial surgery | Lesion mechanism | Strasberg's classification | Immediate surgery | Other procedures |
|---|---|---|---|---|---|---|---|
| 1 | M | 37 | OC | Resection | E2 | Nonrecognized BDI | PBD |
| 2 | M | 59 | OC | Thermal lesion | E3 | Nonrecognized BDI | (1) Bile duct resection + HJ, (2) PBD + PD |
| 3 | F | 55 | OC | Ligature, RHA lesion | E2 + vascular | Nonrecognized BDI | (1) Choleperitoneum- abdominal drainage, HJ (2) PBD |
| 4 | F | 53 | OC | Ligature | E2 | HJ | PBD |
| 5 | M | 32 | OC | Section | E3 | Repair after T-tube placement | (1) HJ (2) PBD |
| 6 | M | 52 | OC | Section, RHA lesion | E3 + vascular | Nonrecognized BDI | (1) T-tube placement, (2) HJ, (3) PBD + metallic stent |
| 7 | M | 40 | OC | Section | E3 | Repair after T-tube placement | (1) HJ, (2) PBD |
| 8 | F | 54 | OC | Section | E3 | HJ | (1) PBD (2) re-HJ |
| 9 | M | 44 | OC | Resection | E3 | Nonrecognized BDI | (1) HJ, (2) percutaneous drainage of hepatic abscess, (3) PBD |
| 10 | M | 41 | OC | Stenosis post T-tube placement | E2 | Nonrecognized BDI | (1) T-tube replacement, (2) PBD |
| 11 | F | 62 | LC | Clipping, section and right pedicle thermal lesion | E4 + vascular | Conversion. Right portal vein ligation. Nonrecognized BDI | (1) Choleperitoneum - abdominal drainage, (2) PBD, (3) HJ |
| 12 | M | 55 | LC converted for BDE | Stenosis post T-tube placement, RHA lesion | E3 + vascular | Nonrecognized BDI | (1) T-tube replacement, (2) HJ, (3) PBD, (4) several replacements due to haemobilia |
| 13 | F | 40 | LC | Resection, termal lesion | E4 | Nonrecognized BDI | (1) HJ, (2) PBD, (3) PD with extraction of intrahepatic stones |
| 14 | F | 29 | RH | Left bile duct section, LHA lesion | N/C + vascular | Nonrecognized BDI | (1) HJ, (2) PBD |
| 15 | F | 26 | HC | Formaldehyde injection | N/C | Nonrecognized BDI | (1) Choleperitoneum - abdominal drainage |
| 16 | F | 46 | HC | Resection | E3 | Nonrecognized BDI | (1) HJ, (2) re-HJ |
| *Patients that died on the waiting list* | | | | | | | |
| 17 | F | 60 | OC | Resection | E4 | Nonrecognized BDI | PBD |
| 18 | M | 43 | OC | Resection | E4 | Nonrecognized BDI | PBD |
| 19 | M | 41 | OC | Stenosis post T-Tube placement | E2 | Nonrecognized BDI | PBD |
| 20 | M | 45 | OC | Resection | E4 | HJ | PBD |

OC = open cholecystectomy; LC = laparoscopic cholecystectomy; BDE = bile duct exploration; RH = right hepatectomy; HC = hydatid cyst resection; RHA = right hepatic artery; LHA = left hepatic artery; PBD = percutaneous biliary drainage; HJ = hepaticojejunstomy; PD = percutaneous dilatation; N/C = not classified

**Table 4** Pretransplantation features

| | Main symptoms | TB | DB | ALP | PT | Child | Meld score |
|---|---|---|---|---|---|---|---|
| 1 | UGB, cholangitis, refractory ascites, pruritus | 13.4 | 9.0 | 1,250 | 55 | B | 20 |
| 2 | UGB, cholangitis | 5.8 | 4 | 630 | 60 | A | 14 |
| 3 | Refractory ascites, pruritus, hypersplenism | 0.6 | 0.2 | 149 | 87 | A | 8 |
| 4 | Cholangitis, pruritus, intrahepatic lithiasis | 9.9 | 5.9 | 644 | 80 | B | 22 |
| 5 | UGB, cholangitis, hepatic abscess | 6.2 | 4.8 | 22 | 80 | B | 17 |
| 6 | Cholangitis, pruritus | 17.4 | 14.6 | 973 | 92 | A | 12 |
| 7 | Cholangitis | 5.5 | 4.3 | 1,000 | 65 | B | 13 |
| 8 | UGB, cholangitis, pruritus, hypersplenism | 10.1 | 6 | 780 | 70 | B | 18 |
| 9 | UGB, cholangitis, hepatic abscess, refractory ascites | 3.2 | 2.4 | 24 | 60 | B | 17 |
| 10 | UGB, cholangitis, refractory ascites, pruritus | 11.3 | 6.0 | 1,035 | 50 | B | 18 |
| 11 | UGB, refractory ascites | 2.4 | 1.2 | 450 | 73 | B | 19 |
| 12 | Cholangitis, intrahepatic lithiasis, hemobilia | 33.0 | 22.0 | 299 | 90 | C | 24 |
| 13 | UGB, intrahepatic lithiasis | 0.8 | 0,.3 | 1,600 | 88 | A | 8 |
| 14 | Cholangitis, refractory ascites, pruritus | 3.2 | 2.3 | 1,100 | 72 | B | 21 |
| 15 | Cholangitis | 6.8 | 5 | 1,823 | 80 | B | 17 |
| 16 | UGB, cholangitis, refractory ascites, pruritus, recurrent SBP | 4.5 | 3.6 | 1,200 | 71 | A | 11 |

UGB = upper gastrointestinal bleeding; SBP = spontaneous bacterial peritonitis; TB = total bilirubin; DB = direct bilirubin; ALP = alkaline phosphatase; PT = prothrombin time

**Table 5** Postoperative complications

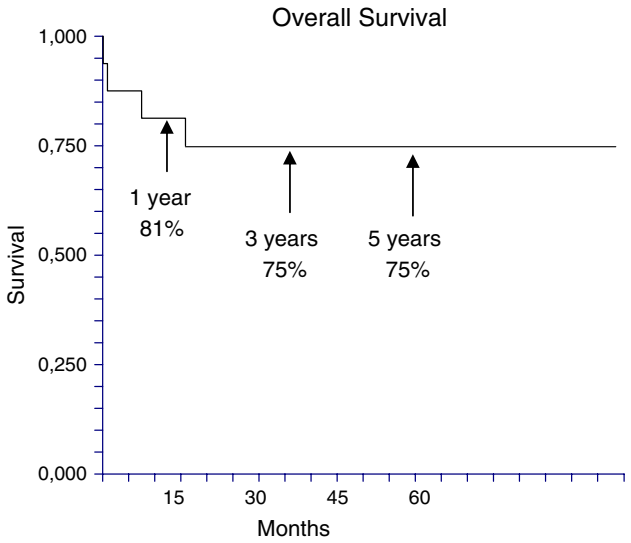
| Postoperative complication | No. of patients | Treatment | Dindo's classification [19] |
|---|---|---|---|
| Intraabdominal abscess | 2 | Percutaneous drainage | IIIB |
| Hemoperitoneum | 2 | Relaparotomy | IIIB |
| Wound infection | 2 | Drainage (1) | II |
| | | Surgical toilette (1) | IIIB |
| Acute rejection episodes | 5 moderate 1 severe | Methylprednisone IV bolus | II |

particularly demanding surgery because the biliary ducts are thin and it is sometimes necessary to perform a deep dissection in the hepatic pedicle. In addition, when reparative surgery is scheduled in the days immediately after the occurrence of injury, local inflammation and fibrosis may make it difficult to determine the precise extent of the lesion and negatively affect the outcome of the anastomosis.

The presence of biliary peritonitis has been described as an independent factor of poor outcome [12]. In our series, seven of the lesions were diagnosed due to such a presentation. A nondiagnosed arterial lesion, the incidence of which is reported at 7-61%, can result in poor outcome of primary treatment [12, 20, 29–32]. Koffron et al. [33] showed that the percentage of vascular lesions is related to the level of the lesion. This incidence reaches 17% in E2 lesions, 44% in E3 lesions, and 39% in E4 lesions [18]. We cannot confirm these findings with our data because only five patients presented an associated vascular lesions (E2, 1; E3, 2; E4, 1; not classified, 1). Regardless of the level of the lesion, vascular injuries are associated with greater mortality and morbidity [32].

The inexperience of the surgeon who performs the operation is another factor associated with poor outcome after primary repair [29–37]. In 33–78% of the cases, primary repair is performed at the same center where the lesion occurred [8, 13, 26, 27, 36, 38]. In our series, all patients except one underwent attempted repair of the biliary tract at the primary center. Patients with complex BDI often undergo several repair attempts before successful resolution. This affects their quality of life and has a high psychological, physical, and mental impact due to the prolonged, complicated, and unexpected nature of the injury [39, 40].

Successive failures of therapeutic procedures or the use of inappropriate treatments may determine the manifestation of late complications such as portal hypertension and secondary biliary cirrhosis [12, 13, 15, 41]. Because of such late complications, 3-20% of the patients with complex lesions should be put on the waiting list for a liver transplant as the only possible treatment [12–16, 20]. Prolonged biliary obstruction can lead to progressive liver fibrosis and secondary biliary cirrhosis. Duration of obstruction is the most important predictor of advanced fibrosis [42]. Johnson et al.




| Time | Patients at risk |
|---|---|
| 12 months | 13 |
| 24 months | 12 |
| 36 months | 9 |
| 48 months | 9 |
| 60 months | 7 |

**Fig. 1** Survival rate after liver transplantation

[8] reported that development of hepatic fibrosis is associated with a delay in the implementation of adequate therapeutic procedures for the treatment of biliary stenosis. Negi et al. [42] found that the mean duration of biliary obstruction before onset of portal and periportal fibrosis was 3.8 months, for the development of severe fibrosis 22.4 months, and for cirrhosis 62 months. The presence of cirrhosis at the time of surgery increases postoperative morbidity and mortality, worsens repair outcome, and results in greater late mortality, even in patients with patent hepaticojejunostomy [43–45]. The presence of marked fibrosis, with consequent resistance in hepatic microcirculation, together with hepatocyte hyperplasia leads to portal hypertension. In fact, 13 of the patients in our series had grade II-III esophageal varices and 9 of them were included for transplantation due to repeated episodes of variceal bleeding. While portal hypertension accounts for 7.3% of all the bile duct injuries treated at our institution, other authors report higher rates [20, 24, 42], with a global mortality rate of 26% [20]. In our series, 4 of the 20 patients that died while on the waiting list had severe portal hypertension resulting in multiple episodes of variceal bleeding. It has also been observed that portal hypertension is an independent factor associated with hospital mortality. Chapman et al. [20] observed a mortality rate of 23% and 2% for patients undergoing surgery with and without portal hypertension, respectively.

The main indication for liver transplantation is advanced chronic liver disease with no alternative form of therapy. Other indicators for liver replacement include intractable ascites, progressive jaundice, repeated episodes of variceal bleeding, repeated episodes of cholangitis, intractable pruritus, and poor quality of life [17].

There are few publications about liver transplantation secondary to a BDI. Some report a small series of cases in which the indication for transplantation was fulminant hepatic failure secondary to an associated vascular lesion [46–49]. However, publications about the development of biliary cirrhosis secondary to a BDI are uncommon [10–16]. According to the European Liver Transplantation Registry, secondary biliary cirrhosis accounts for 1% of all the indications for transplantation (378 patients) [50], whereas in Argentina it accounts for 2% [51].

Previous surgical procedures may adversely affect liver transplantation by increasing both the technical complexity and the risk for complications [10]. In 2002, we published a comparative study of eight patients who underwent liver transplantation for BDI and a control group. In that series we found that patients with BDI had more prolonged and demanding surgery and required more blood transfusions, although postoperative morbidity and the long-term results were similar in both groups [16]. In the present work, the postoperative complication rate, the mortality rate, and the 5-year survival rate were 56.2, 12.5, and 75%, respectively, results equivalent to those observed for transplants undertaken for other diseases.

Interestingly enough, in this study two of the three deaths that occurred during follow-up were due to cancer. Similar results were observed by other investigators who showed an increased incidence of malignant diseases in immunosuppressed patients [11, 52]. In general, this is a group of young patients who were initially operated on for a benign condition [5].

In summary, according to literature, BDI continues to occur worldwide but is not decreasing in frequency [21, 22]. Correct management is essential to ensure long-term survival of patients because inadequate procedures, multiple interventions performed by inexperienced surgeons, and delayed referrals to specialized centers may result in late complications. Secondary biliary cirrhosis and portal hypertension cause significant morbidity and mortality rates, requiring liver transplantation as the only possible treatment. This procedure, for end-stage complicated BDI, is extremely difficult and has a significant postoperative morbidity. Although it provides long-term survival and good quality of life, it represents a high biological price for the patient with a benign disease.

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