Liver transplantation for the sequelae of intra-operative bile duct injury

E de Santibañes, J Pekolj, L McCormack, J Nefa, J Mattera, J Sivori, C Bonofiglio, A Gadano and M Ciardullo

Hepato Bilio Pancreatic Surgery and Liver Transplant Unit, General Surgery Service, Hospital Italiano, Buenos Aires, Argentina

Background

Intra-operative bile duct injuries (IBDI) are potentially severe complications of the treatment of benign conditions, with unpredictable long-term results. Multiple procedures are frequently needed to correct these complications. In spite of the application of these procedures, patients with severe injuries can develop irreversible liver disease. Liver transplantation (LT) is currently the only treatment available for such patients, but little information has been published concerning the results of LT.

Methods

Eight patients with LT for end-stage liver disease for IBDI were studied retrospectively. They had failure of multiple previous treatments and experienced recurrent episodes of cholangitis, oesophageal variceal bleeding, severe pruritus, refractory ascites and spontaneous peritonitis.

Results

Mean recipient hepatectomy time was of 243 minutes (range 140–295 min), the complete procedure averages 545 minutes (260–720) and intraoperative red-blood-cells consumption was 6.5 units (1–7). One patient required reoperation due to perforation of a Roux-en-Y loop, and three developed minor complications (2 wound infections, 1 inguinal lymphocele). One patient died due to nosocomial pneumonia (mortality rate 12.5%). One patient required retransplantation due to delayed hepatic artery thrombosis. At follow-up 75% of patients are alive with normal graft function and an excellent quality of life.

Conclusions

LT represents a safe curative treatment for end-stage liver disease after IBDI, albeit a major undertaking in the context of a surgical complication in the treatment of benign disease. The complications of the surgical procedure and the long-standing immunosuppression impart a high cost for resolutions of these sequelae but LT represents the only long-term effective treatment for these selected patients.

Keywords

liver transplantation, bile duct injury, laparoscopic cholecystectomy

Introduction

Intra-operative bile duct injuries (IBDI) usually occur in young patients during surgical treatment of benign diseases and represent potentially severe complications with unpredictable long-term results [1–3]. Multiple procedures are frequently needed to correct these complications. In recent years, endoscopic and percutaneous procedures have been useful for resolving biliary obstructive complications, prolonging survival and optimising the patient’s condition before receiving definitive treatment [4–6].

Despite application of these procedures, patients with severe injuries develop irreversible liver disease. Chronic cholestasis, recurrent cholangitis and progressive liver fibrosis leading to portal hypertension are the main problems that lead to ill health and premature death. These patients have also refractory pruritus and disabling malnutrition, with multiple hospital admissions and a poor quality of life [2, 6, 7]. Liver transplantation (LT) is currently the only treatment available for such patients. However, little information has been published in the international literature concerning LT in patients with previous IBDI since the beginning of the liver transplantation programmes [8–11]. This study reports our experience with LT as definitive therapy for 8 patients with end-stage liver disease secondary to IBDI.
Patients and methods
Between January 1988 and July 1998, 14 patients with end-stage liver disease secondary to IBDI were considered for LT. Among them, 3 died on the waiting list (from septic and haemorrhagic complications), 8 were successfully transplanted and 3 are still waiting for LT. End-stage liver disease was found in 14 of 84 patients (16.6%) with IBDI referred to our Unit. The 8 transplanted patients represent 3.6% of the 221 LTs performed at our hospital during this period.

The clinical characteristics and outcome of the transplanted patients were analysed retrospectively. There were four men and four women, and the mean age was 41 years (24–62 yr). In 5 patients the IBDI occurred during cholecystectomy (3 open, 2 laparoscopic), in 2 patients during treatment for a hydatid cyst (Figure 1), and in one patient during open common bile duct exploration. The last case was one of instrumental perforation of the posterior wall of the common duct during stone removal. There was one case of complete ligature of the right hepatic vascular pedicle with delayed right lobe liver atrophy (Figures 3 and 4).

Several open and percutaneous procedures were performed in these patients (Figure 2). However, all but one patient had marked strictures of their repairs at the time that LT was indicated. In one case of formalin injury to the bile duct during operation for hydatid cysts, biliary reconstruction was not possible because of the diffuse injury.

The mechanism and level of biliary injury (according to Bismuth’s classification of benign biliary stricture [7]), the reparative procedure and other characteristics of the 8 transplanted patients are described in Tables 1 and 2.

All patients had oesophageal variceal bleeding secondary to portal hypertension, and six received intensive endoscopic therapy (sclerotherapy or banding) and medical treatment. Six patients had multiple episodes of acute cholangitis, one case being associated with multiple liver abscesses. Four patients had refractory ascites, two had intractable pruritus and one patient had recurrent episodes of spontaneous bacterial peritonitis. In patients with gastrointestinal bleeding and/or refractory ascitis, the possibility of a transjugular intrahepatic portosystemic shunt (TIPS) was considered, but this therapy was contraindicated because of the risk of cholangitis and sepsis. LT was performed electively in 7 patients and urgently in one. The mean interval time between IBDI and inclusion on the waiting list was 41.8 months (14–76 ms), and the mean interval time between the last bile duct repair and inclusion on the waiting list was 26 months (9–44 ms). The mean time on the waiting list was 10.6 months (2–23 ms). The average follow-up time after LT was 47.5 months (7–97 ms).

A standard technique was used for vascular reconstruction. Biliary tract reconstruction was performed with a Roux-en-Y hepatojunostomy, with interrupted polypropylene 6/0 or 7/0 sutures and extraluminal knots using expanded field magnification glasses. Bacterial and fungal prophylaxis was given using ceftriaxone plus ampicillin in newly-admitted patients or vancomycin, imipenem and fluconazole in hospitalised patients.

### Table 1. Mechanism of injury, primary biliary repair and other operations in patients transplanted for the sequelae intraoperative bile duct injury

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Set</th>
<th>I Pro</th>
<th>Injury mechanism</th>
<th>Primary repair</th>
<th>Other surgeries</th>
<th>BC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>62</td>
<td>F</td>
<td>Lap Chole</td>
<td>Section. Ischemia. Electrocoagulation</td>
<td>Bi HJA</td>
<td>Laparotomy for choleperitoneum + redo Bi HJA</td>
<td>III + RVL</td>
</tr>
<tr>
<td>2</td>
<td>42</td>
<td>M</td>
<td>Lap Chole</td>
<td>Section</td>
<td>End to end anastomosis T tube</td>
<td>HJA</td>
<td>III</td>
</tr>
<tr>
<td>3</td>
<td>32</td>
<td>M</td>
<td>Open Chole</td>
<td>Section</td>
<td>End to end anastomosis T tube</td>
<td>HJA</td>
<td>III</td>
</tr>
<tr>
<td>4</td>
<td>40</td>
<td>F</td>
<td>Lap Chole</td>
<td>Electrocoagulation</td>
<td>HJA</td>
<td>Laparotomy for choleperitoneum + PBD &amp; stricture dilatation</td>
<td>III–IV</td>
</tr>
<tr>
<td>5</td>
<td>41</td>
<td>M</td>
<td>Open Chole</td>
<td>Section. Ischemia. Electrocoagulation</td>
<td>End to end anastomosis T tube</td>
<td>Choledochopasty + PBD &amp; metallic stent placement</td>
<td>II</td>
</tr>
<tr>
<td>6</td>
<td>24</td>
<td>F</td>
<td>Open Hydatic</td>
<td>Formalin injury</td>
<td>HJA + hemigastrectomy</td>
<td>Laparotomy for choleperitoneum</td>
<td>–</td>
</tr>
<tr>
<td>7</td>
<td>41</td>
<td>M</td>
<td>Open CBDE</td>
<td>Perforation</td>
<td>Percutaneous drainages of AA + PBD &amp; stricture dilatation</td>
<td>II</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>46</td>
<td>F</td>
<td>Open Hydatic</td>
<td>Resection</td>
<td>HJA + Re-HJA</td>
<td>III</td>
<td></td>
</tr>
</tbody>
</table>

Initial procedure (I Pro): Laparoscopic cholecystectomy (Lap Chole) or Open Cholecystectomy (Open Chole); Open Common Bile Duct Exploration (Open CBDE), Bismuth classification of biliary injury (BC); Percutaneous biliary drainage (PBD); Right hepatic vascular lesion (RVL); Abdominal abscess (AA), Hepaticojejunostomy anastomosis (HJA)
Sequelae of bile duct injury

The operative time and intraoperative blood loss in patients transplanted for IBDI (Group I) was compared with that of 116 adult patients undergoing LT for other reasons with a full-size cadaveric liver during the same period in our unit (Group II). Student’s t-Test was used, and significance was established at a p value of 0.05 or less.

Results

In all eight transplanted patients a full orthotopic cadaveric graft was used, according to standard techniques. All transplants were blood group compatible (7 isogroup and 1 heterogroup). Immunosuppressive therapy consisted of cyclosporin, steroids and azathioprine in 4 patients and tacrolimus with steroids in the other four.

The mean recipient hepatectomy time was 243 minutes (140–295 min), the mean time of the anhepatic phase was 89.2 (45–135 min) and 3 patients required extra-corporeal circulation. The mean duration of operation was 545 minutes (270–720 min) compared with 466 minutes (215–900 min) in group II, but the difference was not statistically significant (p < 0.3). Mean operative blood loss was 6.5 (1–7 units) in Group I and 4.4 (0–25 units) in Group II (p < 0.16, ns). Intraoperative accidents included a diaphragmatic laceration in one patient and multiple perforations of the small bowel in another, each related to the release of intense adhesions. There were no intra-operative deaths.

Immediate postoperative complications related to the procedure were peritonitis due to perforation of the Roux-en-Y loop, subphrenic abscess and wound infection, in one patient. Two patients developed mild infection of the surgical wound and one inguinal lymphocele with lymphatic fistula related to the placement of the venous line for the veno-venous bypass. There were no complications related to the biliary anastomosis. Four patients had acute rejection episodes that were mild in three cases and severe in one case. All responded to conventional therapy.

The average weight of the resected specimens was 2151 g (r 1670–2505), and the pathological diagnosis was secondary biliary cirrhosis in five patients and secondary sclerosing cholangitis in three patients (Figure 5).

The in-hospital mortality rate was 12.5%. One patient died on the seventh postoperative day with autopsy evidence of a bacterial pneumonia but no graft complications. The average postoperative stay in the intensive care unit was 6.5 days (4–10 days), and the average postoperative stay in hospital was 19.2 days (11–37 days).

On long-term follow-up, one patient died 7 months after the initial transplant due to rupture of a cerebral mycotic

### Table 2. Laboratory data and indications for LT in patients with IBDI.

<table>
<thead>
<tr>
<th>Case number</th>
<th>Bil t/d (µmol/L)</th>
<th>AP (U/dl)</th>
<th>Prot (%)</th>
<th>Clinical aspects</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>41/20.5</td>
<td>450</td>
<td>73</td>
<td>PHT and recurrent episodes of EVB</td>
</tr>
<tr>
<td>2</td>
<td>94/73.5</td>
<td>1000</td>
<td>65</td>
<td>Recurrent episodes of cholangitis</td>
</tr>
<tr>
<td>3</td>
<td>73.5/46.2</td>
<td>1020</td>
<td>80</td>
<td>Recurrent episodes of cholangitis</td>
</tr>
<tr>
<td>4</td>
<td>13.7/5.1</td>
<td>1600</td>
<td>88</td>
<td>Multiple liver abscesses</td>
</tr>
<tr>
<td>5</td>
<td>193.2/102.6</td>
<td>1035</td>
<td>50</td>
<td>PHT with recurrent episodes of EVB</td>
</tr>
<tr>
<td>6</td>
<td>167.6/109.4</td>
<td>1823</td>
<td>80</td>
<td>Recurrent episodes of cholangitis</td>
</tr>
<tr>
<td>7</td>
<td>229.1/153.9</td>
<td>1250</td>
<td>55</td>
<td>PHT with recurrent episodes of EVB</td>
</tr>
<tr>
<td>8</td>
<td>76.9/61.6</td>
<td>1200</td>
<td>71</td>
<td>Refractory ascitis</td>
</tr>
</tbody>
</table>

Total and direct serum bilirubin (Bil t/d); Alkaline phosphatase U/dl (AP); Prothrombine concentration (Prot.) Esophageal variceal bleeding (EVB); Portal hypertension (PHT).
aneurysm after retransplantation for thrombosis of the hepatic artery. The remaining 6 patients (75%) have a very good quality of life and normal liver function tests.

Discussion

Although technical and technological advances allow a better solution for IBDI, the future of these patients is not yet well defined. Many patients receive endoscopic and percutaneous procedures as initial treatment to avoid reparative surgery. The long-term results of such procedures have not yet proved their effectiveness. Some patients present frequent episodes of cholangitis and persistent cholestasis, as shown by liver function tests. Persistent elevation of serum alkaline phosphatase indicates a variable degree of biliary obstruction, a mechanism that generates progressive and irreversible chronic disease in 8–10% of cases [4–6, 12].

One of the most frequent causes of secondary biliary cirrhosis (SBC) and secondary sclerosing cholangitis (SSC) is benign stenosis of the bile duct, which is generally due to a surgical injury [13]. In a series of 44 patients reported by Braasch, the incidence of SBC after bile duct repair for intraoperative injuries reached 8% on long-term follow-up [3].

The causes of irreversible liver disease and its complications such as SBC are a poor initial repair of the lesion, multiple strictures and anastomotic obstruction with persistent cholestasis. Cholestasis causes biliary portal and centrilobular ectasia. To become established cirrhosis, cholestasis must persist for a considerable period of time, yet liver disease does not develop in all cases. This variable behaviour could be accounted for by the complete or incomplete nature of the biliary obstruction, by the existence of accessory biliary canals or by reperfusion with the formation of new ducts surrounding the obstruction [14, 15]. In the one patient with injury of the formalin biliary tree, the time from the initial lesion to the indication for transplant was only 14 months because of recurrent episodes of cholangitis.

Special considerations should be kept in mind concerning LT in patients with end-stage liver disease secondary to IBDI. Complications such as intractable pruritus, recurrent life-threatening cholangitis or severe impairment of nutritional status may become the main indication for LT. From a technical standpoint there is additional risk because of previous surgical and instrumental procedures [13].

In a series of 130 patients with IBDI, 17.7% had portal hypertension and in all those who died in hospital (6.2%), death resulted from the complications of portal hypertension or from liver failure and sepsis [1]. Biliary tract injuries are frequently associated with hepatic artery and portal vein lesions, and these factors worsen the prognosis [8, 9]. In our IBDI series, 3 patients died on the waiting list as a consequence of intractable complications of portal hypertension complications, and one patient had an injury of the right arterial and portal pedicle which led to complete atrophy of that lobe [10].

We have not found any published series of patients transplanted as a consequence of IBDI, although some reviews mention LT as a therapeutic possibility [2]. In one recent publication on IBDI, however, LT was not even mentioned as an option for treatment [12]. Two case reports have been published of patients with biliary and vascular injury following laparoscopic cholecystectomy who required LT [8, 9]. Likewise, many worldwide series of transplants, SBC cases are exceptional. In Bismuth’s report of 350 patients, only three patients were transplanted for SBC, and the cause of this complication was not described [13].

In 1990, Moossa published a report of a series of 81 patients with IBDI including four who had been transplanted, all of whom died in the postoperative period. In the discussion of this paper, Block suggests ‘… patients were transplanted too late, or were transplanted at a very early stage in the development of this type of surgery’ [2].

Intractable ascites, repeated episodes of variceal bleeding, repeated cholangitis, progressive jaundice, pruritus and poor quality of life are all indicators for the need of liver replacement [13, 16]. Early referral to transplant centres is recommended to avoid severe malnutrition and infectious complications before the procedure, a situation that becomes worse with a long waiting period (three of our patients died waiting for a liver). Treatment of malnutrition and concomitant infections is required during this period. Percutaneous biliary procedures are helpful in the treatment of pruritus and acute cholangitis in this stage [16].

In these patients LT is technically more complex than usual, due to intra-abdominal adhesions, sclerosis of the hepatic pedicle, severe portal hypertension and associated coagulopathy. Profuse bleeding may be encountered during the heptectomy phase, and in cases of severe portal hypertension veno-venous bypass may be necessary to minimise this bleeding. Cannulation of the portal system through the inferior mesenteric vein is useful before dissection of the hepatic pedicle in such cases. In our series the intraoperative blood loss and total operation time were higher than in LT for other reasons, but not significantly so.
The five-year survival rate of LT for benign diseases exceeds 80%, with excellent quality of life. For this reason, we believe that the use of this procedure to treat end-stage liver disease for IBDI will increase in the future. For optimal results, LT must be performed soon after the development of severe sequelae.

The advent of laparoscopic cholecystectomy has led to a resurgence of IBDI. Moreover, these lesions have proved to be more severe and complex that those caused during open cholecystectomy. They tend to be located more proximally (in association with resection of the bile duct) and may be combined with external biliary fistulas that result in a small-calibre bile duct at the time of initial surgical repair. Short-term results may therefore be poor after repair, while concomitant vascular injuries make the situation even worse [4–6, 8, 9, 12]. All these facts lead us to suggest that IBDI during laparoscopic cholecystectomy will result in an increased demand for LT in the future [6].

References