Alternative transplant procedures for acute liver failure

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Abstract

Acute liver failure (ALF) is associated with significant morbidity and mortality. The outcome is highly unpredictable and recovery depends on several factors. Patients can deteriorate with increasing encephalopathy, coagulopathy and progress to multiorgan failure (MOF). In such patients, liver transplantation (LT) is the only current potential cure. Orthotopic liver transplantation remains the standard procedure for LT in ALF, **however, other surgical options have been explored. This review summarises the use of a variety of alternative transplant procures for the treatment of acute liver failure including** : **Two stage OLT, Auxiliary liver transplant, Living donor liver transplantation (LDLT), and ABO incompatible liver transplant.** (Acta gastroenterol. belg., **2010**, 73, **374-379**).

Key words : Acute Liver Failure, Acetominophen induced liver failure, Orthotopic Liver Transplant, Two Stage Liver Transplant, Auxiliary Liver Transplant, Live donor Liver Transplant, Live Donor Auxiliary Liver Transplant, ABO incompatible Liver Transplant

Introduction

The syndrome of acute liver failure (ALF) results from the abrupt loss of metabolic and synthetic hepatic function. It clinically manifests with coagulopathy and encephalopathy and can rapidly progress to multiorgan failure (MOF) (1). In the UK, Europe and USA, acetaminophen (paracetamol) toxicity is the leading cause of ALF, whereas infectious hepatitis (A, B and E) constitutes the most common cause worldwide (1,2,3). ALF is associated with significant morbidity and mortality. The outcome is highly unpredictable and recovery depends on several factors including the underlying aetiology, age of the patient, duration of time over which the disease develops, the extent of liver damage and the early institution of supportive care (3).

Patients with severe ALF are usually referred to a tertiary centre for specialist care. Supportive therapy continues in the hope of spontaneous recovery which can occur, especially with acetaminophen toxicity in up to 90% of patients (4). However, a small number of patients continue to deteriorate with increasing encephalopathy and coagulopathy, progressing to MOF. In such patients liver transplantation (LT) is the only current potential cure. Selection for LT in most units is based on the Kings College Criteria for ALF. In the US, around 5% of LTs are performed for ALF and 25-30% of patients with ALF proceed to LT (1,2). The number of patients selected for LT varies widely between different aetiologies. Patients with acute Wilson's disease or fulminant seronegative hepatitis are more likely to be listed for transplantation than those with drug-induced ALF and hepatitis A infection. This is due to the increased chance of spontaneous recovery in the latter (3).

Orthotopic liver transplantation (OLT) remains the standard procedure for LT in ALF. However, other surgical options have been explored and these are discussed below.

Orthotopic liver transplant

Data from the European Transplant Registry (ELTR) shows that OLT in acute liver failure has a 1-year, 5-year and 10-year survival rate of 69%, 63%, 58% respectively (5). This data is consistent with a recent single centre retrospective study by Marudanayagam *et al.*, analysing 1327 with ALF over a 16 year period (3). They found that of 1327 patients with ALF, 327 were listed for OLT (21.3%). 263 patients received a graft (80.4%). 184 patients who received a graft are still alive. The overall survival was 70% with a median survival of 57 months (range : 0-197 months). The 1-year, 5-year and 10-year survival rates were 76.7%, 66%, 47.6%, respectively. The 30 day mortality rate was 21.6%. Re-transplantation was performed in 11.8% of patients, the main reasons being chronic rejection and hepatic artery thrombosis (3).

OLT remains the standard form of LT in ALF, with reasonably consistent survival rates worldwide.

Two stage orthotopic liver transplant

In standard OLT, the recipient operation is divided into two stages : hepatectomy and implantation. Usually, these steps are done sequentially within the same session in order to keep the anhepatic phase as short as possible. However, there are situations in which these stages have to be divided and the implantation phase delayed. It has been observed that patients with failing livers may be better off anhepatic rather than having a necrotic liver *in situ*, which has a very high mortality (approaching

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100%). Patients can have complete reversal of unresponsive shock upon total hepatectomy. Therefore, the failing liver can be removed, a portocaval shunt fashioned to allow venous decompression and postpone the implantation until a suitable graft found. This was first performed by the Hanover group in 1986 and they published results of 32 patients treated in this manner in 1993 (6). The primary objective was to treat patients with non functioning grafts and haemodynamic and renal instability. These fatal complications are a consequence of hepatic necrosis. The full-blown picture is equivalent to 3- or 4-organ failure, which can be well circumscribed by the term "toxic liver syndrome". This is characterised by complete liver necrosis associated with cardiovascular shock, renal and possibly respiratory failure. Twelve patients had primary hepatectomies (no previous LT) and 22 had a secondary hepatectomy (LT carried out but failed due to rejection or primary non function). Thirteen of their patients were unable to proceed to OLT and rapidly died from MOF. The maximum anhepatic survival time was 34.5 hours. Nineteen patients had the second stage OLT and 10 survived. The nonsurvivors died of sepsis or acute respiratory distress syndrome. Three of the 10 survivors had a late death (112 days, 3 months and 22 months) (6).

Oldhafer *et al*. published data for the same procedure, but the exclusive indication was PNF following OLT. They found that hepatectomy reduced the need for vasopressive agents and improved pulmonary function in the majority of patients. Four patients died before a liver was available. Sixteen patients received OLT after 19.82 ± 15.34 hr (range 6.58 to 72.50 hr). Two of the 16 transplanted patients died on the first postoperative day due to multiorgan failure and pneumonia. The remaining 14 of 16 patients survived retransplantation, but 7 died between days 13 and 105 mostly due to sepsis. Seven patients were well at discharge and showed long-term survival (7).

The University of Essen group published the same strategy for 8 patients. For 5 patients the indications were bleeding secondary to liver rupture, 2 patients had hepatic necrosis as a complication of biliary surgery and 1 patient had carbon tetrachloride poisoning. Two of the 8 patients died as a result of uncontrollable bleeding before a donor was available. Five of the six patients that did receive grafts died postoperatively. One patient survived and remained alive 6 years on from the surgery (8).

A more recent paper from Brazil reports 3 cases in which this two stage procedure was performed. Two patients had primary non function following OLT and subsequently had had hepatectomies. They received grafts and one of the patients was a long term survivor, the other was discharged, but then re-admitted and died with MOF 72 days following re-OLT. The other patient had ALF due to Wilson's disease and was haemodynamically unstable with severe intracranial hypertension. She developed toxic liver syndrome and subsequently had a hepatectomy, but showed no improvement. She died 8 hours following hepatectomy (9).

A report by Montalti *et al.* had 4 patients who underwent total hepatectomy with portocaval shunts for various indications. The mean anhepatic phase was 19.25 hours. Interestingly, all 4 patients survived the two stage transplantation procedure without major complications (10).

This concept of total hepatectomy is very useful when considering treatment of ALF. As stated by Ringe *et al.*, the acutely failing liver produces a toxic syndrome and removal of the liver can lead to immediate haemodynamic stability and general improvement of the patient's condition (6). Adapting this concept, partial hepatectomy in ALF, may help to reduce the toxic burden and improve patient haemodynamics without completely removing the native liver. As many cases of ALF are reversible, a transplant could bridge the gap whilst native liver function recovers.

Auxiliary liver transplant

With standard OLT, patients commence life-long immunosuppression and are continually at risk of developing complications from it, and also complications from the graft itself. Auxiliary liver transplantation (ALT) aims to eliminate immunosuppression in the long term by using a transplant as a bridge to allow time for native liver regeneration. Once enough function is established immunosuppression can be withdrawn and the transplant atrophies. The advantages are obvious in the form that there needs to be no further monitoring of the patient and no immunosuppression related complications. It is also of benefit to patients who are non-compliant, as is the case with many patients who develop ALF secondary to acetaminophen toxicity.

There are three described techniques for ALT. Heterotopic auxiliary liver transplantation (HALT) involves placement of a graft below the native liver. This method requires implantation on to the infrahepatic vena cava and sufficient space in the abdomen. This technique, despite some success, yielded poor results and subsequently auxiliary partial orthotopic liver transplantation (APOLT) has been used more widely and accepted as a standard technique for ALT. It involves resection of the native liver (left or right hemihepatectomy) and the placement of a split graft in an orthotopic manner. The third technique is based on APOLT, but the recipient undergoes right hepatic trisectionectomy and whole graft implantation (WGALT) in an orthotopic manner.

The advantages of APOLT and WGALT over HALT can be linked to the two stage strategy. Ringe *et al.* showed that hepatectomy for toxic liver syndrome resulted in improved haemodynamics (6). Therefore a subtotal hepatectomy will reduce the amount of necrotic liver tissue and subsequently reduce the effects of toxic liver. At the same time the transplant will provide hepatic function until sufficient native regeneration has taken

place. The question that arises is how much liver can we safely remove?

Van Hoek *et al.* described 47 patients who underwent ALT for ALF between 1986 and 1995. Indications varied and 35 patients received APOLT and 12 HALT. They demonstrated a 1 year survival rate of 62% with ALT (vs 61% OLT control group). However, the HALT group had a 1 year survival of 33% compared with 71% for APOLT. There were 7 re-transplants, 4 by OLT, 2 APOLT, 1 HALT. Three of 4 OLT survived, 1 re-APOLT survived (the other died a 6 days) and the re-HALT died (11 days). The 1 year re-transplant free survival for OLT vs APOLT was 52% and 60%. In 15 of the 40 ALTs, the graft was removed and immunosuppression withdrawn. Nine of these patients were alive at one year post ALT. Six died following graft hepatectomy for graft necrosis. Of the 25 with the graft *in situ*, immunosuppression was stopped in 6 and the graft allowed to atrophy. The group concluded that APOLT offers an advantage over OLT in ALF in terms of a chance of a life free of immunosuppression without jeopardising the chance of overall survival (11).

Azoulay *et al.* compared 30 patients with ALF treated by OLT against 12 patients treated by APOLT. In hospital deaths for APOLT were 33%, compared with 25% for OLT. There were increased rates of technical problems with APOLT compared with OLT. Neurologic sequelae persisted in 3 of the 12 APOLT group compared with 1 of 24 in the OLT group. The need for retransplantation was significantly higher in the APOLT group (3/12 vs 0/24). Seven of the 12 patients showed signs of liver regeneration but only 3 of these went on to withdrawal of immunosuppression. One died 1 month after graft removal which means only 2 of the APOLT patients had full success. The authors concluded that the complication rate was high with APOLT compared with OLT and on an intent to treat basis, OLT had a higher efficacy (12).

Jaeck *et al.* reported 17 patients who underwent 18 APOLT procedures. Three patients were retransplanted with OLT and one using a left auxiliary graft. Six deaths occurred, 5 due to septic complications. Native regeneration occurred in 11 of 17 patients (65%) and in 8 of the 11 survivors (74%). Five of these have ceased immunosuppresion (13).

A study by Quaglia *et al.* had a cohort of 49 patients undergoing APOLT for ALF. At the time of review, 38 (77.6%) patients were alive and 20 (52.6%) were off immunosuppression. Six patients were being weaned off immunosuppression and 8 remained on full immunosuppression. Four (8.2%) underwent OLT after removal of the native liver. Eleven (22.4%) patients died at a median of 31 days post ALT. They demonstrated that in up to 62.5% of patients the native liver regenerates to full recovery. In such patients immunosuppression can be reduced and in the vast majority (80%) it can be discontinued altogether. They conclude that acetaminophen toxicity is an excellent indication for ALT with full native recovery occurring in 100% of surviving patients (14).

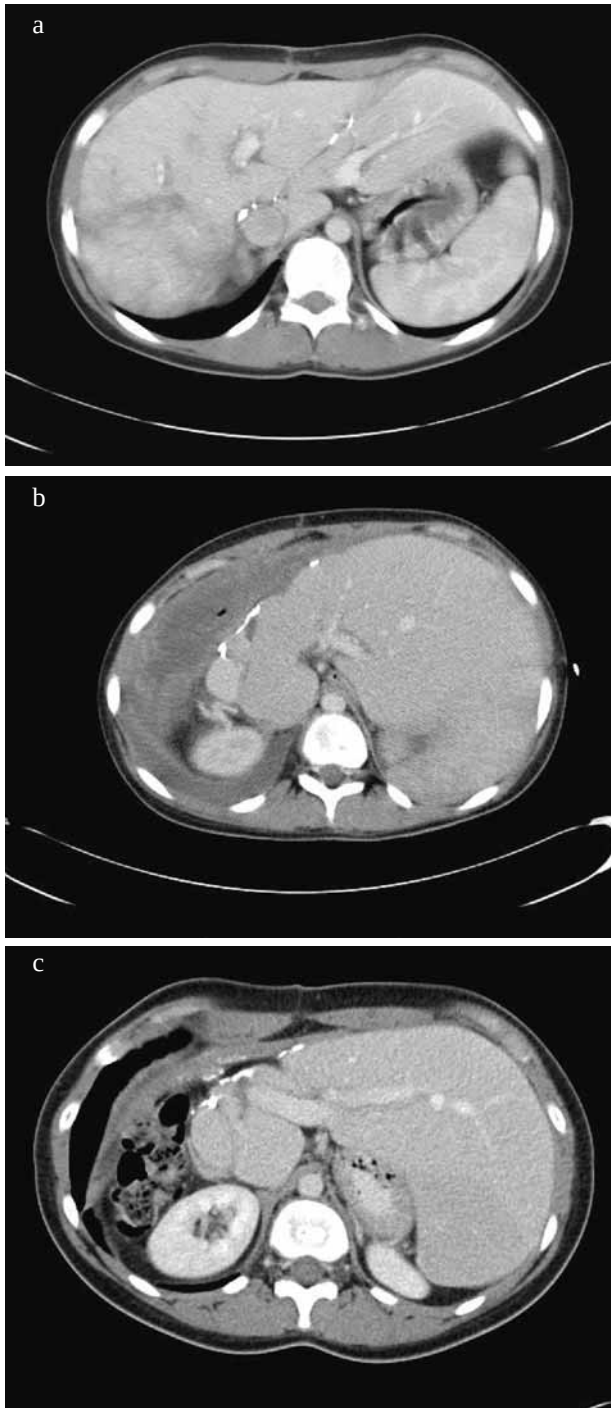

Fig. 1. — CT scans showing native liver regeneration and transplant liver atrophy after withdrawal of immunosuppression.

(a) At start of immunosuppression withdrawal (5 months post transplant in this case) with a 3 month withdrawal protocol.
(b) At 11 months post transplant and off immunosuppression
(c) At 2 years (16 months after last immunosuppression dose). The spleen has moved down due to the hypertrophy of the native left lobe. The right kidney has risen slightly due to the increased space in the right upper quadrant

Our group in Leeds have reported on whole graft ALT (WGALT) combined with a subtotal hepatectomy (right hepatic trisectionectomy), comparing 13 cases with 13 OLT with favourable results in the ALT group (15). We have now performed 22 WGALT exclusively for acetaminophen toxicity. Of the 22 patients, 15 have survived (68%), and all patients had sufficient regeneration to cease immunosuppression (Figure 1). Of the 7 deaths, 6 occurred within 10 postoperative days, the other at 60 days. Two deaths occurred after PNF and subsequent OLT. One patient required OLT due to hepatic artery thrombosis and continues to do well. One patient required graft hepatectomy for sepsis at 6 weeks post WGALT, but had sufficient native regeneration. Another patient required graft hepatectomy for abscess at 8 months post WGALT. One patient had a non heart beating (DCD) donor and is fairing well, but has developed a biliary stricture in his native liver. In conclusion, we have shown success of WGALT for acetaminophen induced ALF. Right trisectionectomy removes a large proportion of native necrotic liver, thereby reducing the toxic load further than conventional hemihepatectomy as in APOLT, but leaving sufficient native liver for regeneration. Following withdrawal of immunosuppression, all patients had normal liver function. In this drug toxicity induced ALF subgroup, ALT may be more suitable as future drug compliance is not an issue.

Live donor liver transplant

Living donor liver transplantation (LDLT) has been widely accepted as an alternative treatment of choice for ALF. The largest experience comes from Japan, Hong Kong and Korea, as live donation is virtually the only source of organs in these regions.

Ikegami *et al.* report a 10 year experience of LDLT for ALF. A total of 42 patients with ALF underwent LDLT, including 3 paediatric patients. Aetiology of ALF included hepatitis B, hepatitis C, autoimmune hepatitis, Wilson's disease and unknown causes. The grafts varied : left lobe (n = 9), left lobe plus caudate lobe (n = 24), right lobe (n = 8), and lateral segment (n = 1). The 1- and 10- year survival rates were 77.6% and 65.5% respectively for grafts and 80% and 68.2% respectively for patients (16).

Matsui *et al.* performed 36 LDLT for ALF over an 11 year period (in the same time 366 patients underwent LDLT for chronic liver disease). Aetiology was HBV-related ALF, Autoimmune hepatitis, Wilson's disease and unknown in 23 cases. There was a total of 23 complication (64%). Two patients required re-transplantation, one for PNF and the other for HAT. Intraperitoneal bleeding occurred in 5 patients (14%) and 4 required a laparotomy. There were 12 (33%) patients who had acute rejection. Four patients (11%) were complicated by hepatic artery thrombosis, two (6%) with portal vein thrombosis, and 1 (3%) with stenosis of the hepatic venous anastomosis. All of these patients required surgical revision and all but one graft were saved, the latter requiring retransplantation. There was a 17% bile leak rate and 22% rate of anastomotic strictures. Patient and graft survival rates at 1- 3- and 5-years were 97%, 87%, 87% and 91%, 82% and 82% respectively (17).

Hiramatsu *et al.* had 50 consecutive patients with ALF over a 6 year period. Of those, 29 were offered LDLT. There was no suitable donor for 12 patients and only 3 of these patients survived. The remaining 17 patients had suitable donors. Ten patients underwent LDLT, 8 survived (80%). Of the remaining 7, 4 improved and 3 passed into a critical condition during the waiting period and died (18).

Campsen *et al.* performed 10 LDLT for ALF over a 9 year period. All patients received a right lobe graft. They had a 70% survival rate and no patient underwent retransplantation. Importantly, no patient awaiting LT died prior to transplantation (19).

Kilic *et al.* performed 14 LDLT for ALF in six adults and 8 children. Right lobe grafts were used for adults. 11 of the 14 were alive at the time of reporting, with 1- and 3-year survival of 79%. This was better than the 1- and 3-year survival rate of 58% for patients who received grafts from deceased donors at the same centre. Deaths occurred due to sepsis in two patients at 1 and 3 months following transplantation. The third patient died due to aplastic anaemia 6 months after transplantation (20).

Uribe *et al.* performed 16 LDLT for ALF in children and compared results with 27 cadaveric donors. 18.7 % of the LDLT group required regraft (2 HAT, 1 PNF) vs 26% amongst the cadveric group. They report no mortality or serious morbidity in the LDLT group (21).

Live donor auxiliary liver transplant

Kobayashi *et al.* performed 5 auxiliary live donor transplants for ALF since February 2003. Three patients had unknown aetiology, one had Wilson's and the other hepatitis B. APOLT was performed in 3 patients and HAPLT in 2. All recipients underwent small for size grafts. In all but one case (APOLT) a left sided graft was used. The other was a right sided graft. Three of five patients survived. One patient (HAPLT) died on postoperative day 2 with pneumonia, and the other 10 months following APOLT due to sepsis. There were technical complications in all five patients including, bleeding, requiring re-laparotomy, abdominal compartment syndrome requiring a skin flap, re-hepaticojejunostomy for biliary ligation during donor surgery. Biliary strictures were seen in two patients. Only one patient came off immunosuppression (22).

ABO incompatible liver transplant

ABO incompatible grafts have been associated with a high risk of rejection, vascular thrombosis and bile duct complications. Recent experiences have shown up to

60% 5-year survival due to new immunosuppression protocols, plasmapheresis and use of splenectomy (23).

Uribe *et al.* described 3 cases of ABO incompatible grafts in the setting of ALF. Two patients had group A livers to O recipients and 1 group A to B recipient. They all had plasma exchange and splenectomy. All three patients were alive at the time of reporting, however, 1 patient had acute cellular rejection which responded to methylprednisolone, and another required retransplantation (with a compatible donor) after 7 days (24).

Banz *et al.* reported a case in which a patient with acetaminophen toxicity underwent ABO incompatible APOLT. A left lobe split was used along with plasmapheresis. The patient's condition improved and intracranial pressure values stabilised until another group matched donor was found. The patient then underwent re-OLT and remained well 15 months after transplantation (25).

Summary

Acute liver failure is a serious condition with a highly unpredictable outcome and significant morbidity and mortality. OLT is the standard treatment for patients who require liver transplantation. However, there are other surgical options available for the treatment of ALF. Patients with some aetiologies for ALF do have the ability to recover their native liver function and bridging the period of recovery with ALT is definitly possible as shown in the above studies. The main advantage of ALT over OLT is the complete withdrawal of immunosuppression. This not only reduces the side effects and complications from immunosuppression, but prevents the need for continual long term follow up. Ultimately, if the patient can retain their native liver, they will have an improved quality of life (15). The advantages of hepatectomy have been shown initially by Ringe *et al.* (6). Our own series showed that right trisectionectomy can successfully reduce the toxic load of the necrotic liver, yet still leave enough native liver to allow full recovery and return to normal liver function. Using whole graft auxiliary transplantation can also reduce complications as there is only one cut liver surface and there is less of a question about having enough liver parenchyma to support the patient with ALF.

Live donor transplantation is used to treat ALF with varying results. It works well in paediatric patients as they do not usually suffer the small for size syndrome that adults may get from receiving a split graft. There are limited studies using live donor auxiliary liver transplantation for the treatment of ALF, but small for size syndrome may be a problem in this setting. Dual grafts have been used to combat this situation, but its feasibility as a routine tool is questionable.

Aetiology of ALF does impact the outcome. Those with acetaminophen induced ALF may have a better chance of recovery from ALT, as we know that the native liver recovers well. However, patients with viral causes (except Hepatitis A) may not do as well, because of the potential for relapse and incomplete recovery.

With the shortage of donor organs, many avenues have been explored for the treatment of ALF. Standard OLT remains the mainstay of treatment. However, in selected patients ALT may offer an improved result with a better quality of life.

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