Subtotal hepatectomy and whole graft auxiliary transplantation for acetaminophen-associated acute liver failure

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Abstract

Background: An acetaminophen overdose (AOD) is the leading cause of acute liver failure (ALF) in the UK and USA. For patients who meet the King’s College Hospital criteria, (mortality risk > 85%), an emergency orthotopic liver transplantation (OLT) is conventionally performed with subsequent life-long immunosuppression. A new technique was developed in 1998 for AOD-induced ALF where a subtotal hepatectomy (right hepatic trisectionectomy) and whole graft auxiliary liver transplant (WGALT) was performed with complete withdrawal of immunosuppression during the first year post-operatively.

Results: During 1998–2010, 68 patients were listed for an emergency transplantation for AOD ALF at our institution: 28 died waiting, 16 underwent OLT and 24 a subtotal hepatectomy with WGALT. Eight OLT (50%) and 16 WGALT remain alive (67%); actuarial survival at 5 years OLT 50%, WGALT 63%, \( P = 0.37 \).

All patients who had successful WGALT are off immunosuppression. Poor prognostic factors in the WGALT group included higher donor age (40.4 versus 53.9, \( P = 0.043 \)), requirements for a blood transfusion (4.3 versus 7.6, \( P = 0.0043 \)) and recipient weight (63.1 versus 54 kg, \( P = 0.036 \)).

Conclusion: Although OLT remains standard practice for AOD-induced ALF, life-long immunosuppression is required. A favourable survival rate using a subtotal hepatectomy and WGALT has been demonstrated, and importantly, all successful patients have undergone complete immunosuppression withdrawal. This technique is advocated for patients who have acetaminophen hepatotoxicity requiring liver transplantation.

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Introduction

Acute liver failure (ALF), defined as the presence of hepatic encephalopathy and coagulopathy in patients with no history of liver disease, is the result of an abrupt loss of both hepatic metabolic and immunological function, and in many cases can rapidly progress to multi-organ failure.1–3 The aetiology of ALF is diverse including viral, autoimmune and drug-related causes.1–3 An acetaminophen overdose (AOD) is the predominant cause of ALF in the UK and USA and the overall mortality in this group is as high as 28%.4–6 Patients with AOD-induced ALF who meet King’s College Hospital (KCH) criteria have a mortality risk of more than 85% without emergency liver transplantation.5,7 The overall 5-year survival rate after an orthotopic liver transplantation (OLT) for AOD-induced ALF is reported to be up to 67%.5,6 However, OLT results in the need for life-long immunosuppression and in the AOD patient group there are concerns about psychological and/or psychiatric problems that can make adherence to treatment unmanageable, even with full social support.8

To minimize the risks of poor compliance and also reduce the long-term risks of immunosuppression associated with OLT, an auxiliary liver transplantation (ALT) may be considered as an alternative. With AOD-induced ALF, time and appropriate supportive therapy give the potential for full hepatic recovery. With this notion, an auxiliary liver transplant can be used to bridge the gap to give the native liver time to recover. Once sufficient native liver function has returned, immunosuppression can be withdrawn and the transplanted liver allowed to atrophy.

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Our institution performs more than 250 solid organ transplants and over 300 liver resections annually, and has the largest reported experience worldwide with hepatic trisectionectomy.\textsuperscript{9,10} The senior author developed a new technique in 1998 in which a right hepatic trisectionectomy was performed as a subtotal hepatectomy combined with whole graft auxiliary liver transplant (WGAL T) for AOD-induced ALF, and initial results were reported in 2008.\textsuperscript{11} In this study, the largest reported series is presented and the long-term results are demonstrated.

**Methods**

During January 1998 to July 2010, 24 patients underwent a subtotal hepatectomy with WGAL T for AOD at our institution. Patients referred for further management after AOD from other UK hepatology and gastroenterology centres were commenced on medical therapy prior to transfer. Patients were listed for ‘super-urgent’ liver transplantation based on KCH criteria for AOD.

**Surgical principles**

The surgical principles and techniques have been described in detail previously.\textsuperscript{11} In summary, after a right hepatic trisectionectomy (resection of liver segments 4, 5, 6, 7 and 8), a whole graft is implanted in an orthotopic manner. Caval anastomosis is performed using a donor upper end to recipient side cavo-cavostomy, with suture closure of the lower donor IVC. The donor portal vein is anastomosed end to end to the recipient right portal vein. Arterial anastomosis was initially to the recipient right hepatic artery but after early hepatic artery thrombosis in case 3 it has been performed using a conduit from the right common iliac or external iliac artery. A Roux-en-Y hepaticojejunostomy to the donor CBD/CHD is performed to avoid any risk of strictureing the recipient biliary tree.

**Donor liver policies**

According to our policy for super-urgent OLT, there was no donor selection bias in that the first liver offered nationally was accepted.
in all cases. All re-transplants (for WGALT failure) were performed as OLT with resection of the remaining native liver remnant.

**Withdrawal of immunosuppression**

Immunosuppression consisted of cyclosporin or tacrolimus combined with corticosteroids and azathioprine or mycophenolate mofetil, according to our standard protocol for OLT at that time. Corticosteroids were withdrawn within 12 weeks of transplantation in all patients. At 3 months post-operatively, a hepatic iminodiacetic acid (HIDA) and computerized tomography (CT) scan were used to judge recovery in the native liver. At this stage, a full discussion with each patient was carried out to obtain consent for immunosuppression withdrawal and azathioprine/mycophenolate mofetil was discontinued. The calcineurin inhibitors were reduced by one-third dose every month. The aim was to discontinue all immunosuppression by 6 to 12 months. Liver function tests and clinic reviews were the only monitoring during immunosuppression withdrawal. A CT was performed at 6 months to confirm atrophy of the graft and hypertrophy of the native liver. All patients were followed up closely during immunosuppression withdrawal and on an annual basis once immunosuppression was completely withdrawn.

**Data analysis**

Patient and donor characteristics analysed included listing pH, prothrombin time (PT), serum creatinine, recipient/donor

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**Table 1** Summary of recipient and donor data for all 24 WGALT patients with outcomes

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (years)</th>
<th>Gender</th>
<th>Weight (kg)</th>
<th>Listing PSE</th>
<th>Listing pH</th>
<th>Listing PT (s)</th>
<th>Listing creatinine (μmol/l)</th>
<th>Donor age</th>
<th>Donor weight (kg)</th>
<th>Donor-recipient weight ratio</th>
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<td>60</td>
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<tr>
<td>2</td>
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<td>M</td>
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<td>253</td>
<td>36</td>
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</tr>
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</table>

*Denotes supported (CVVH, blood products).
PSE, portosystemic encephalopathy; creatinine 88.4 μmol/l = 1 mg/dl; Op, during surgery; HAT, hepatic artery thrombosis; PNF, primary non-function, HV thrombus, hepatic vein thrombus; ReTx, re-transplant; CMV, cytomegalovirus; CVVH, continuous veno-veno-haemofiltration; DCD, donation after cardiac death; POD, post-operative day; Normal values; pH 7.35–7.45, PT 10–14 seconds; creatinine, 60–120 mmol/l.
weight, cold ischaemia time (CIT), blood product requirement (up to 48 h post surgery), immunosuppression withdrawal and survival.

**Statistical analysis**
SPSS version 17.0 (SPSS Inc., Chicago, IL) was used to calculate means and standard deviations, using the independent *t*-test and Mann–Whitney *U*-test for comparison. The significance was set at *P* < 0.05. Survival curves were calculated using the Kaplan–Meier method.

**Results**

**Patients**
During January 1998 to July 2010, 207 patients received a liver transplant for ALF and 40 of these, were for AOD. There were a further 28 deaths in AOD patients awaiting a liver transplant. Of the 40 AOD patients, 24 received a WGALT and 16 underwent OLT (Fig. 1). Patient selection for WGALT depended on the on-call surgeon’s preference and enthusiasm for this novel procedure as not all surgeons in our unit had embraced the concept, with the senior author performing 23 of the 24 WGALT procedures. There was no bias in patient selection for the procedure.

In the OLT group there were 12 females and 4 males, aged 18 to 52 years (mean 37). In the WGALT group there were 14 females and 10 males, aged 18 to 50 years (mean 31.5). Table 1 shows patient and donor factors along with outcomes after WGALT. There was little variation between patients selected for WGALT over OLT, as seen in Table 2. APACHE scores between the two groups were not statistically different. A higher donor weight was the only significant finding in the OLT group.
Survival
Currently, 16 of 24 patients remain alive after WGALT. The 1-year survival rate was 71%. Of the 8 patients that died, 6 died within 10 post-operative days, one died at 60 days and another at 23 months after WGALT: the overall survival was 67%. Three patients required a re-graft in the form of OLT (2 primary non-function – died and 1 hepatic vein thrombosis – alive) giving a re-transplant rate of 12.5%. Thus 15 of the 24 patients (63%) remain alive with a native liver remnant. The actuarial 1-, 3- and 5-year survival rates for successful WGALT patients \((n = 15)\) was 70%, 65% and 65%, respectively (Fig. 2). In the OLT group, there are 8 remaining survivors (50%) with an actuarial 1-, 3- and 5-year survival rates of 69%, 63% and 50%, respectively. Of the eight patients that died, there was one on-table death after reperfusion, three deaths in the ICU, one owing to cerebral oedema, two due to sepsis and multi-organ failure, one patient developed hepatic artery thrombosis and developed sepsis (patient was at a different institution), one patient developed post-transplant lymoproliferative disorder and died 2 years after transplant, and two deaths were as a result of chronic rejection related to poor compliance. Of the survivors, three developed renal impairment, two of which remain chronic. There were no regrafts performed in the OLT group (0%). There was no significant difference in survival between the OLT and WGALT groups, \(P = 0.43\) (log-rank test).

Withdrawal of immunosuppression
Immunosuppression withdrawal was successful in all patients who survived without re-transplantation (a total of 15 patients). During immunosuppression withdrawal, minor elevations in liver enzymes were noted, but in the absence of systemic symptoms. Liver function tests normalized within 3 months of immunosup-

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**Table 2** Comparison of factors between patients who underwent whole graft auxiliary transplant (WGALT) versus those who underwent orthotopic liver transplantation (OLT)

<table>
<thead>
<tr>
<th></th>
<th>WGALT ((n = 24))</th>
<th>OLT ((n = 16))</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recipient age</td>
<td>31.1 (9.1)</td>
<td>29.4 (9.8)</td>
<td>0.588*</td>
</tr>
<tr>
<td>Donor age</td>
<td>44.3 (15.1)</td>
<td>45.4 (15.4)</td>
<td>0.817*</td>
</tr>
<tr>
<td>Recipient weight (kg)</td>
<td>66.4 (11.7)</td>
<td>65.7 (9.7)</td>
<td>0.847*</td>
</tr>
<tr>
<td>Donor weight (kg)</td>
<td>61.0 (9.8)</td>
<td>69.1 (10.3)</td>
<td>0.019*</td>
</tr>
<tr>
<td>Weight ratio</td>
<td>0.93 (0.19)</td>
<td>1.06 (0.18)</td>
<td>0.036*</td>
</tr>
<tr>
<td>Listing pH</td>
<td>7.19 (0.13)</td>
<td>7.23 (0.07)</td>
<td>0.215*</td>
</tr>
<tr>
<td>Listing PT</td>
<td>100.1 (57.1)</td>
<td>128.6 (26.0)</td>
<td>0.334*</td>
</tr>
<tr>
<td>Listing creatinine (µmol/l)</td>
<td>276.2 (127.2)</td>
<td>273.9 (83.7)</td>
<td>0.911*</td>
</tr>
<tr>
<td>Preservation time (min)</td>
<td>472 (150)</td>
<td>583 (169)</td>
<td>0.825*</td>
</tr>
<tr>
<td>Blood (units)</td>
<td>5.3 (3.6)</td>
<td>7.7 (7.0)</td>
<td>0.338*</td>
</tr>
<tr>
<td>FFP (units)</td>
<td>12.3 (4.7)</td>
<td>16.3 (8.5)</td>
<td>0.166*</td>
</tr>
<tr>
<td>Platelets (units)</td>
<td>10.7 (8.8)</td>
<td>13.7 (8.3)</td>
<td>0.214*</td>
</tr>
</tbody>
</table>

*Independent t-test statistic.
*Mann–Whitney U-test statistic.

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**Figure 2** Kaplan–Meier survival curve for 24 patients who underwent whole graft auxiliary transplant (WGALT) compared with 16 who had orthotopic liver transplantation (OLT). WGALT survival (green) demonstrates better survival than the OLT (blue) group.
pression cessation. In 4 patients, late WGALT graft abscesses occurred which presented with sepsis. Two patients were treated by percutaneous drainage and 2 required WGALT hepatectomy.

**Native liver regeneration**
In the surviving patients who had a successful WGALT (n = 15), all had good native liver regeneration and WGALT atrophy. Figure 3 demonstrates sequential CTs of a WGALT patient over a 2-year period.

**Recipient and donor data**
Table 3 shows a comparison of the patients who survived for over a year against those who died. Statistically significant factors upon univariate analysis included higher donor age (40.4 versus 53.9, P = 0.043) and blood transfusion requirements (4.3 versus 7.6, P = 0.043). Multivariate analysis revealed recipient weight was the only significant factor affecting outcome (63.1 versus 54 kg, P = 0.036).

**Complications**
There were seven early post-operative deaths, six of which occurred within 10 post-operative days. In summary, two patients died as a consequence of graft primary non-function in spite of re-transplantation by OLT; two patients died secondary to an intracranial haemorrhage; two patients died as a result of sepsis (at 4 and 60 post-operative days); and 1 patient died owing to acute AOD-induced lung injury and cardiac failure.

Specifically, the following significant complications occurred. Patient 2 died owing to acute AOD-induced lung injury and...
cardiac failure. Patient 3 developed WGALT hepatic artery thrombosis at 12 days and required a graft hepatectomy at 4 weeks, with immediate immunosuppression withdrawal. After this case, the decision was taken to to perform future WGALT (cases 5–24, case 4 having already been done) using an iliac arterial conduit (as aortic clamping caused hemodynamic instability). Patients 7 and 8 both had primary non-function and were re-transplanted using OLT. However, both these patients died within 10 post-operative days. Both of these patients had received livers from older donors (age 65 and 69 years). Patient 11 initially recovered then died from an intracranial haemorrhage on day 5. Patient 12 developed WGALT hepatic vein thrombosis and underwent a completion hepatectomy and OLT on day 16. Patient 14 died from sepsis on day 4. Patient 18 died after 2 months from sepsis, gastrointestinal bleeding and acute tubular necrosis in spite of haemofiltration. Patient 19 who was known to have hepatitis C as well as AOD, received a DCD (donation after cardiac death) graft and progressed well initially, but developed abnormal liver function while off immunosuppression. He was found to have an exacerbation of hepatitis C and alcoholism with progression to cirrhosis and died 23 months after ALT. Patient 20 was unresponsive after WGALT. A CT scan confirmed cerebral oedema and tonsillar herniation. Patient 22 was noted to have a left-sided weakness once she had been extubated and a CT scan confirmed an intracranial bleed. At 6 weeks, WGALT hepatic artery thrombosis occurred and a graft hepatectomy was performed. All symptoms from her stroke have now resolved.

Discussion

An acetaminophen overdose (AOD) is the leading cause of acute liver failure in the UK and USA. The patients are usually young, predominantly female and may have previous and ongoing psychological issues. Although the majority will recover with medical management, those who fulfill KCH criteria may be listed for emergency liver transplantation. OLT has yielded good short-term results and the long-term outcomes are less favourable. Adherence to outpatient follow-up and immunosuppression is poor in the AOD group compared with other groups of patients who have undergone OLT. This may relate to poor patient selection and this remains difficult as these patients are critically ill and usually intubated on arrival at the transplant centre. A liver resection with auxiliary liver transplantation (ALT) aims to maintain some native liver, and transplant a whole or partial graft to allow temporary hepatic support. After an unspecified time, immunosuppression can be withdrawn and this is associated with an improved quality of life compared with OLT.

In AOD, hepatotoxicity is a direct liver injury caused by the toxic metabolite of acetaminophen. With an overdose, gluturonyltransferases and sulfotransferases are saturated diverting the drug to be metabolized by cytochrome P450 and generating N-acetyl-p-benzo-quinoneimine (NAPQI) in amounts that can deplete glutathione. If glutathione is not replenished, NAPQI will begin to accumulate in the hepatocytes, leading to an increase in levels of cytosolic calcium and ultimately loss of membrane integrity. There is evidence that AOD can cause mitochondrial dysfunction, eventually leading to an alteration of membrane permeability and release of mitochondrial proteins into the cell cytoplasm, and oncotic necrosis of hepatocytes. There is also alteration of the innate immunity of the liver as cell death caused by toxic metabolites activates Kupffer cells and phagocytic macrophages of the liver to release cytokines that may activate natural killer cells. These may contribute to further liver damage by cytotoxic activity. Inflammatory mediators, cytokines and chemokines, recruit and accumulate neutrophils in the liver and exacerbate the hepatic injury. This process leads to development of hepatic necrosis which can be fatal and is well circumscribed by the term ‘toxic liver syndrome’. This is characterized by complete liver necrosis associated with cardiovascular shock, renal and respiratory failure. Yet, even in severe acetaminophen-induced ALF, the liver damage usually resolves spontaneously with appropriate treatment in up to 90% of cases, with less than 10% requiring liver transplantation. In patients who recover without OLT, there appears to be no long-lasting liver damage.

It has been observed that in AOD-induced ALF patients, a complete hepatectomy can lead to short-term reversal of unresponsive shock. It has been postulated that a partial hepatectomy may have similar effects if a large enough amount of the ‘toxic burden’ is removed. Further, as the liver injury is fully reversible, implantation of a donor liver may allow temporary support while the native liver remnant recovers.

There are three described techniques for auxiliary liver transplantation (ALT): heterotopic auxiliary liver transplant (HALT), auxiliary partial orthotopic liver transplant (APOLT) and whole graft auxiliary transplant (WGALT). HALT involves leaving the native liver in situ and placing a whole or split graft in a heterotopic position, but HALT has yielded poor results. APOLT involves resection of a portion of liver and placement of a corresponding split graft in an orthotopic manner. Results have generally been reasonable, although few patients have completely ceased immunosuppression.

Emergency transplantation outcomes are consistently poorer than those of elective transplantation, with high early post-transplant mortality, mainly as a result of sepsis, neurological complications and multi-organ failure. Patients with acetaminophen-induced ALF usually have a greater severity of illness than seen in ALF from other causes and this is reflected in a higher 30-day post-transplant mortality of around 25%. Our 1-year survival of 71% is equal to that of studies of OLT in AOD induced ALF. Excellent long-term survival rates have been achieved and there was only one late death at 23 months in a patient with hepatitis C and alcoholism (67% patient survival, 63% native liver survival). Importantly, we have shown that after transplantation, native regeneration is present in 100% of survivors and liver function is restored, with all eligible patients off
immunosuppression. Previous studies have shown that native recovery does not occur in all cases of ALF, but this relates to aetiology.16–18

A previous controversy relating to ALT was the functional competition resulting from the portal blood flow shared by the graft and the native liver.19–21 Various techniques have been applied to overcome this problem, but in this series, we have not observed any portal blood flow competition and we have described the reasons for this previously.11 APOLT usually involves a hemihepatectomy or less and has the disadvantage over WGALT of leaving a greater amount of necrotic liver tissue. In our WGALT the patient undergoes a right hepatic trisectionectomy (removal of segments 4, 5, 6, 7 and 8) which corresponds to greater than 70% of liver mass. Other advantages of our technique include placement of a whole donor graft, ensuring there is maximal liver volume to aid recovery. This avoids any small for size problems potentially encountered in APOLT and gives the patient the best chance of restoration of liver function.22–23 It also reduces the morbidity associated with two hepatic transection surfaces such as bleeding and bile leaks.18 This series is unique in that we have used WGALT exclusively for AOD ALF and not for any other aetiology of acute liver failure. In AOD ALF there is an excellent chance of native liver regeneration, and therefore, a graft can truly bridge the gap between ALF and native liver recovery/regeneration. It was found that donor age, a requirement for a blood transfusion and recipient weight were statistically significant factors related to survival. These have been demonstrated in other previous studies.24–30 However, owing to a small series it is difficult to draw real conclusions and therefore form guidelines based on these findings.

We have had no problems with liver regeneration in our patients: all have had good native liver remnant hypertrophy and have normal liver function in the long term, except for the patient who had established hepatitis C which progressed and was exacerbated by alcoholism. This study has demonstrated that during the first few months post-operatively there is a need for intensive monitoring of these patients. However, once the patient is off immunosuppression, there is little or no follow-up required. It is therefore likely that a subtotal hepatectomy with WGALT in the setting of AOD is more cost effective in the long term than OLT. There were also no problems with chronic renal impairment as noted in the OLT group.

In summary, we advocate the technique of a right hepatic trisectionectomy and whole graft auxiliary liver transplantation for those patients who have acute acetaminophen hepatotoxicity requiring liver transplantation. We are pleased we have achieved our goal of complete immunosuppression withdrawal in all patients where the auxiliary graft provided an effective bridge to recovery. Although a prospective clinical trial now seems justified, the complexity of this patient group means the widespread adoption of this demanding surgical technique will not be achieved unless physicians dealing with AOD-induced ALF recognize its value.

Conflicts of interest
None declared.

References
transplantation (C) The whole liver. (A) I prefer auxiliary liver transplant. J Hepatol 46:570–573.


