

ORIGINAL ARTICLE

Long-term outcome following liver transplantation for paracetamol overdose

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Keywords

complications, liver transplantation, paracetamol overdose, psychiatric complications, renal impairment, survival.

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Paper presented in plenary session at the 13th Annual International Congress of the International Liver Transplantation Society and ATC 2007.

Received: 26 February 2009

Revision requested: 30 March 2009

Accepted: 21 October 2009

Published online: 25 November 2009

doi:10.1111/j.1432-2277.2009.01007.x

Summary

Paracetamol overdose (POD) is a major cause of acute liver failure (ALF) requiring liver transplantation in the United Kingdom. To characterize the early and late outcome after orthotopic liver transplantation (OLT) for POD in the Scottish Liver Transplant Unit over a 14-year period (1992–2006). Data were obtained from a prospective database combined with case-note review. Of 127 liver transplants performed for ALF, 44 were for POD. The median age was 30 (range 18–51). In 18 patients (63.7%), POD was associated with alcohol/other drugs, nine (20.5%) had a staggered overdose and four patients (9.1%) accidentally overdosed. Nineteen patients (43.2%) had a history of previous overdose/psychiatric illness. Post-transplant mortality during the index admission was 30% (13 patients), whilst five patients died during follow-up. The actuarial 5-year patient survival was 54.5%, whilst graft survival was 49.5%. Some 23% of the patients were re-transplanted: primary nonfunction (1), hepatic artery thrombosis (3) and chronic rejection (2). Three patients had a subsequent transplant; three patients had two further transplants. Nine patients (35%) continue to have social/psychiatric issues. OLT for POD is associated with significant early and late morbidity and mortality. A multidisciplinary approach is required to identify the suitable candidates, in whom transplantation should be pursued promptly.

Introduction

Paracetamol is one of the most widely used analgesics in the world because of the lack of adverse effects at therapeutic doses. However, overdosage can lead to acute liver failure requiring liver transplantation [1,2]. In the United Kingdom, paracetamol overdose (POD) is a leading cause for acute liver failure requiring liver transplantation. Although accidental POD does occur, in the majority of cases the overdose is taken with suicidal intent and is often associated with ingestion of other drugs or alcohol [3]. In an attempt to reduce the rate of POD in the United Kingdom, restrictions in the amount of paracetamol that may be bought without prescription have been introduced, although the effects of this measure are not clear [4]. However the number of patients listed for liver trans-

plantation attributable to paracetamol overdose has remained reasonably static and constitutes around 20–30% of those patients transplanted for acute liver failure [5].

Criteria for listing of patients with acute liver failure for liver transplantation are well-defined [6]. In addition to determining the physiological requirement for liver transplantation in POD, the decision to list for transplantation has to be frequently made in the context of psychiatric illness, deliberate suicide attempts, alcohol consumption, associated comorbidity and compliance issues. Such decisions require a multi-disciplinary approach.

Although the short-term results following transplantation for paracetamol overdose have been extensively reported [6–9], there is little data concerning the

long-term outcome in this group of patients and in particular the impact of the liver transplant on survival and the overall usage of a scarce resource. Therefore, the aim of this study was to characterize the early and late outcome after orthotopic liver transplantation (OLT) for paracetamol overdose in the Scottish Liver Transplant Unit over a 14-year period.

Patients and methods

Six hundred and eight patients with paracetamol overdose were managed in the Scottish Liver Transplant Unit between 1992 and 2006. Of these, 436 patients did not meet the King's College criteria for listing and were managed conservatively without consideration of OLT. One hundred seventy-two (28%) patients who met the criteria underwent further assessment to exclude other contraindications to transplantation. The current medical contraindications to transplantation in our unit include: untreated or progressive infection, malignancy, progressive hypotension resistant to vasopressor support, clinically significant acute respiratory distress syndrome (ARDS), fixed and dilated pupils >1 h in the absence of thiopentone therapy, acquired immunodeficiency syndrome (AIDS) and severe coexistent cardiopulmonary disease. Patients also undergo a psychiatric assessment and the current exclusions from transplantation in our unit include: multiple episodes of self harm (>5) within an established pattern of behaviour (especially if non drug methods were used); consistently stated wish to die, in the absence of established mental illness (especially depression); chronic refractory schizophrenia or other mental illness, resistant to therapy; incapacitating dementia or mental retardation; active intravenous drug abuse; active poly-drug use, in a severe chaotic fashion; alcohol dependence or use of alcohol in a severe and chaotic fashion; an established pattern of past noncompliance with medical treatment. Following this assessment, 68 patients were found suitable for transplantation and 44 of them underwent OLT. All patients listed for liver transplantation met nationally agreed listing criteria for POD associated acute liver failure (ALF) which are based on King's College criteria. Demographic, admission and follow-up data were obtained from a prospectively collected database supplemented by case-note review with particular emphasis upon data from outpatient liver transplant and psychiatric follow-up where available. The follow up period was a median of 7 years. Data are expressed as median (range). Kaplan–Meier curves were used to analyse patient and graft survival rates. Statistical analysis was performed using SPSS (version 10; SPSS Inc., Chicago, IL, USA).

Results

Forty-four orthotopic liver transplants were performed during the study period. This represented 35% of the total number of liver transplants for acute liver failure performed in the unit during the 14-year period (Fig. 1). The female to male ratio was 1.2:1 (20 male-, 24 female patients) and the median age at the time of transplant was 30 years (range 18–51 years). Eighteen patients (63.7%) of the 44 who were transplanted took the POD in association with alcohol or other drugs. Nine patients (20.5%) presented following a staggered overdose, that is, the overdose was a consequence of multiple episodes of ingestion of paracetamol over a short period of time in contrast to a single episode of paracetamol ingestion. Nineteen patients (43.2%) had a history of previous overdose or psychiatric illness that was not considered contraindication according to the criteria described previously. Only four patients (9.1%) had an accidental overdose. The median number of reported paracetamol tablets ingested was 50 (25 g) (range 10–125).

At admission to the Scottish Liver Transplant Unit (SLTU), 29 patients (65.9%) were jaundiced, 11 patients (25%) were acidotic with pH < 7.30 (H^+ > 50 nM), 21 patients (47.8%) were encephalopathic (16 patients grade 1–2 and five patients grade 3–4) whilst a further nine patients (20.5%) were already ventilated on admission. The biochemistry and haematology profile on admission to SLTU is shown in Table 1.

As shown in Table 1, most patients had an abnormal renal function and 37 of them (84%) required renal support. 35 patients (79.5%) received continuous venovenous haemofiltration (CVVH) whilst two patients (4.5%) received intermittent haemodialysis (IHH). Only seven patients had a preserved renal function.

All 44 patients met the King's College criteria for transplantation. The median time interval between admission and transplantation was 36 h (range 12.5–156). The

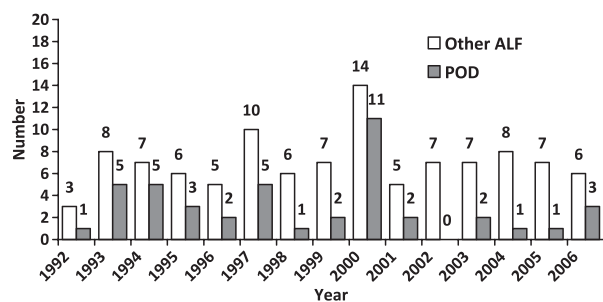


Figure 1 Orthotopic liver transplantation for paracetamol overdose in relation to orthotopic liver transplantation for other causes of acute liver.

Table 1. Haematology and biochemistry profile on admission for the 44 liver transplant recipients (Hb, haemoglobin; WCC, white cell count; ALT, alanine transaminase, GGT, gamma glutamine transaminase).

Admission blood profile	Median (range)
Hb (g/l)	126 (49–225)
WCC ($10^9/l$)	16.3 (6.3–33.5)
Prothrombin time (PT) (s)	70.3 (19–240)
Bilirubin (μm)	85 (28–198)
ALT (U/l)	9490 (694–18269)
GGT (U/l)	46 (20–306)
Alkaline phosphatase (U/l)	95 (26–211)
Creatinine (μm)	198 (54–489)

median stay in intensive care was 7 days (range 1–89) with a median total hospital stay of 26 days (range 2–158).

The mortality rate during the index admission was 30% (13 patients), whilst a further five patients (11%) died subsequently during follow-up. Of the 18 patients who died, three patients had undergone more than one orthotopic liver transplant (one patient died intra-operatively during the second transplant, another died from pulmonary haemorrhage shortly after the second transplant whilst the third one suffered a hepatic artery thrombosis with multiple organ failure following the third transplant). The causes of death (Table 2) were sepsis, liver failure and multi-organ failure which accounted for six deaths (four during the index admission and two afterwards) and cardiovascular events which accounted for six deaths (three cerebrovascular accidents and three cardiac arrests). All deaths were transplant-related except for one case, where malignant melanoma may have been accelerated by immunosuppression.

For patients undergoing OLT for POD, the actuarial 5-year patient survival was 54.5% with a median survival

Table 2. Causes of death for the index admission and during follow-up.

	Index admission (<i>n</i> = 13)	During follow-up (<i>n</i> = 5)
Cardiac intra-operative	2	1 (2nd transplant)
Sepsis/organ failure	4	2
Cerebrovascular	3	0
Hepatic artery thrombosis	1	1
Primary nonfunction	1	0
Peritonitis	1	0
Pulmonary haemorrhage	1	0
Immunosuppression related	0	1

of 11 years, whilst the 5-year graft survival rate was 49.5% with a median survival of 4.2 years. Comparison was made to outcome following OLT within the SLTU for other indications over the same study period. The 5-year survival following liver transplantation for POD is similar to OLT for other causes of ALF (*n* = 59; 5-year patient survival 63% *P* = 0.201; 5-year graft survival 56%, *P* = 0.292). However, when compared to patients undergoing OLT for chronic liver disease (*n* = 467; 5-year patient survival 73.3% *P* < 0.01, log rank test; 5-year graft survival 68%, *P* < 0.01, log rank test) outcomes were significantly worse. Beyond 5 years, patient and graft survival are inferior compared with transplantation for non-POD ALF as well as chronic liver disease (Fig. 2). When the outcome of transplants for POD according to the era of transplantation was compared, there was no difference between the first 7 years and the subsequent 8 years. However, all grafts in the second period were lost during the first month after transplantation. All these patients had a higher lactate on admission and died because of septic complications (3) or as a consequence of POD neurological complications (3).

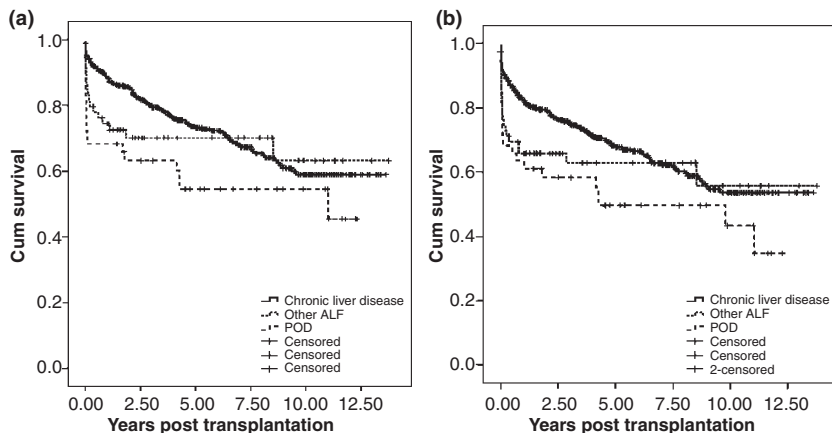


Figure 2 (a) Patient and (b) graft survival curves for liver transplantation for paracetamol overdose, other causes of acute liver failure and chronic liver disease.

Re-transplantation was required for six patients (13.6%). Three patients had a further transplant whilst three other patients underwent two subsequent OLTs. The reasons for retransplantation included primary non-function, arterial ischaemic events (hepatic artery thrombosis, hepatic ischaemia, ischaemic cholangiopathy) and chronic rejection.

The incidence of biliary complications (stricture and/or leakage) was 27%. Four patients (16%) had acute rejection whilst chronic rejection was documented in six patients (23%). To date, nine patients (35%) continue to have documented social or psychiatric issues, namely depression, drug misuse, self-harm and unemployment. Of the 26 patients alive at the end of the study period, only three patients have managed to have no complications or ongoing medical problems at follow-up.

Discussion

Paracetamol overdose accounts for a significant proportion of patients requiring liver transplantation for acute liver failure in the United Kingdom. Although, the incidence of POD in the UK appears to have levelled over the last few years, there is evidence to suggest that within Scotland the incidence remains high when compared with other areas in the UK [10]. Within this study, a large proportion of patients presented with a mixed overdose, where paracetamol was combined with other drugs or alcohol. This illustrates one of the difficulties in managing these patients and in particular deciding their suitability for transplantation namely identifying relevant psychosocial issues that preclude transplantation. Throughout this study, King's College criteria [6] have been used to determine the patient's physiological need for transplantation. In recent years, these criteria have come under scrutiny [11–14] as it was considered that they cannot reliably identify transplant candidates. To address some of these concerns, in the United Kingdom, these criteria have recently been modified [5].

It is important to note that only 28% of the 608 patients managed for POD in the Scottish Liver Transplant Unit met the King's College criteria for transplantation, and only 12% were found to be suitable for transplantation after consideration of comorbidity and psychiatric assessment. Only 7% of patients with POD were transplanted. This in part reflects the complex medical and psychiatric condition of these patients that requires careful and timely assessment whilst avoiding unnecessary delays in a critically ill group of patients. There are definite psychiatric contraindications to transplantation as described previously in the article. A history of previous overdose or psychiatric illness is not necessarily a contraindication to transplantation as shown by this

series, where 43% of those who were transplanted fell in this group. However, in order to achieve good results, it is paramount that the patients undergo a careful multi-disciplinary assessment which should include input from surgeons, hepatologists, intensivists and, most importantly from expert psychiatrists. It is not uncommon that a full psychological assessment is impossible, given that patients are encephalopathic or intubated and therefore the contribution of a psychiatric team routinely involved in the assessment of patients for liver transplantation is essential, to ensure a thorough review of psychiatric history from patient (when possible), family and GP. However, even with expert assessment, within our series at least 35% of patients continue to have significant social or psychiatric issues. This highlights some of the practical and ethical issues surrounding transplantation in patients with POD and the possible need for long-term psychiatric management as well as standard post-transplant follow up.

The management of ALF resulting from POD may be complex and it is our view that it should be undertaken within liver transplant units if possible. Within Scotland, early referral and transfer to SLTU for patients with evidence of liver dysfunction as a consequence of POD is for the most part normal practice. However, even with early referral, this study illustrates that patients with ALF resulting from POD are critically ill and can rapidly deteriorate. Of those patients who underwent OLT, 67% of the patients were encephalopathic or ventilated on admission to the unit. If transfer to a specialist unit is not possible then early referral and close communication with a transplant unit is required in order that appropriate patients do not miss out on a life-saving liver transplant.

Perhaps not surprisingly, the outcome in this group of patients is inferior to those undergoing transplantation for chronic liver disease, but comparable to the survival experienced by other groups of patients with acute liver failure. The poorer outcome in POD transplants and in particular, the high mortality rate post-transplantation reflects the critical condition of these patients. Even with the best supportive therapy pre- and post-transplant, there is a 30% mortality during the index admission with a further 11% of patients succumbing during follow-up. The multi-systemic impact of the overdose and the physiological instability of patients with ALF resulting from POD are illustrated by the fact that multi-organ failure, sepsis and cardiovascular events represent the main causes of death in the peri-operative period. In the second half of this study, all grafts were lost early (within 30 days post-transplant) resulting from multi-organ failure or as a consequence of neurological complications of POD.

Another contributor to the high mortality in this group of patients might have been the quality of the donor

organs. These patients are placed on the national super-urgent transplant list and receive the first available (and usable) graft in the country. Many of these grafts (up to 50% in our recent experience) are marginal. The combination of a very sick recipient and a marginal graft is far from ideal. In an ideal world, one could afford to be more selective in the use of marginal grafts in this situation. However, the urgency of the patient, corroborated with the unpredictability of organ availability and an increased proportion of marginal grafts retrieved, has led to an increased use of such livers for acute liver failure. This was associated with a change in logistics to allow us to minimize the cold ischaemic time in order to reduce the impact of the marginal graft.

There was a higher rate of transplant-related complications such as biliary complications, acute rejection and chronic rejection. In particular, the incidence of biliary complications appears to be significantly higher than the reported overall incidence following transplantation for chronic liver disease in our unit (14.6%) [15] or elsewhere [16].

It is not clear whether the psycho-social issues in these patients contributed to a lack of compliance leading to multiple rejection episodes that ultimately led to the need of re-grafting. However, the nature of this study does not allow any definite conclusions to be drawn about a possible link between on-going psychosocial issues and poor compliance. Furthermore, survival in POD transplants is comparable with that following transplantation for other ALF.

Re-transplantation was required in 14% of cases, and all these patients required multiple grafts. The causes of transplant failure are similar to those seen in the chronic liver disease population. It is difficult to determine the contribution of the underlying psychiatric condition to the development of chronic rejection leading to re-transplantation. However, it was obvious that a significant proportion of the survivors have persistent problems ranging from self-harm and unemployment to drug misuse and depression. Very few of these patients were completely free of complications during the follow-up.

This study provides a 15-year national perspective on transplantation for POD in a country where the incidence of the condition remains high despite previous changes in legislation and as such it provides an interesting comparison with previous reports from the United Kingdom [7,8] and the US [9]. Although the study captures all cases managed in the unit, it may not reflect the true incidence in the general population, as some cases may not be referred to the transplant unit and may be managed by the local teams. Furthermore, as a result of its retrospective nature, data on long-term psychiatric complications and its relationship with chronic rejection could not be completely ascertained.

Although an attempt was made to accurately record the incidence of persistent social or psychiatric problems following OLT for POD, it is likely that there is an element of under-reporting and therefore it is possible that the high level of psychiatric morbidity identified in this study does in fact under-estimate the size of the problem. Nevertheless, the Scottish experience and the outcome following transplantation for POD appear to be significantly different from other published reports from the United Kingdom [17] but are difficult to ascertain whether this is as a result of sicker patients, differences in psychiatric or comorbidity evaluation or the acceptance of more marginal grafts for these patients. Further monitoring as well as an analysis of pooled data is required to establish the reasons for these differences.

Paracetamol overdose patients are a challenge to the transplant community and require difficult decisions to be made by a multidisciplinary team, involving surgeons, hepatologists, intensivists and psychiatrists. Despite the inferior survival and multiple complications, these patients deserve a fair chance of life and transplantation may be the only available option. In those who are identified as suitable candidates, transplantation should be pursued promptly.

Authorship

LRK: performed data collection, statistical analysis and wrote the first draft. GCO and JJP: designed the study, contributed to the statistical analysis and wrote the final version of the manuscript.

Funding

No financial support.

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