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Liver transplantation for fulminant hepatic failure: importance of renal failure

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Abstract One hundred eighty-one consecutive patients with fulminant hepatic failure (FHF) presenting in a 2-year period were reviewed. In this cohort we examined the impact of pretransplant renal failure on mortality and morbidity following orthotopic liver transplantation (OLTx). Twenty-seven patients (18 female, 9 male) with a median age of 43.5 years (range 19–65 years) underwent OLTx. FHF was due to idiosyncratic drug reaction ($n = 4$), paracetamol overdose ($n = 3$), seronegative hepatitis ($n = 17$), hepatitis B ($n = 1$), veno-occlusive disease ($n = 1$), and Wilson's disease ($n = 1$). Renal failure was present in 14 patients, 7 of whom died (whereas there was 100 % survival in patients without renal failure). Pretransplant renal failure was associated with prolonged mechanical ventilation (13 days vs 6 days, $P = 0.05$), prolonged intensive care stay (17 days vs 8 days, $P = 0.01$) and prolonged hospital stay (27 vs 21 days, P = NS). Pretransplant renal failure did not predict renal dysfunction at 1 year after OLTx. We conclude that the survival of patients transplanted for FHF is inferior to that of patients transplanted for chronic liver disease (67 % vs 88 % 1-year survival in Birmingham). For patients with FHF undergoing transplantation, pretransplant renal failure strongly predicts poor outcome with significantly greater consumption of resources.

Key words Fulminant hepatic failure, Renal failure · Liver transplantation ·

Introduction

The pathophysiology of renal failure complicating fulminant hepatic failure (FHF) is thought to be identical to that of the hepatorenal syndrome presenting in end-stage chronic liver disease [23]. Renal pathological findings are minimal and, in both situations, the development of renal failure reflects the severity and advanced stage of the liver disease. Hepatorenal syndrome in the presence of FHF has been shown to be associated with a fatal outcome unless liver transplantation is performed [6]. Patients with hepatorenal failure recover their renal function after orthotopic liver transplantation (OLTx) for chronic liver disease [9].

Long-term renal function after OLTx has been shown to deteriorate in those patients with worse pre-OLTx renal function and is not associated with cyclosporin levels [1]. In this study we wanted to see how the presence of pretransplant renal function influenced the mortality and morbidity after OLTx for FHF and to see if it had any effect on the renal function in survivors after 1 year of follow-up.

Methods

We reviewed a total of 181 patients (106 female, 75 male) with FHF who presented to our center between January 1993 and Janu-

ary 1995 (Table 1). They were referred because of severity of liver dysfunction on the basis of coagulopathy, metabolic acidosis, hypoglycemia, or hepatic encephalopathy. These patients were sedated, paralyzed, and ventilated if they had grade III-IV hepatic encephalopathy and monitored with central venous pressures and with pulmonary artery catheters if hemodynamically unstable.

For the purpose of this analysis, acute renal failure was defined as a serum creatinine greater than 150 mmol/l. Those patients with oliguric renal failure (urine output less than 500 ml/24 h) were started on hemodialysis or hemofiltration. During the period of time under consideration we changed our protocol from continuous arteriovenous hemodialysis (CAVHD) to continuous venovenous hemofiltration (CVVH).

Elevation of intracranial pressure (ICP) was assessed clinically and, in some patients, directly with ICP monitoring; episodes of raised ICP were treated with mannitol infusions, hyperventilation and, in refractory cases, with thiopentone.

Broad-spectrum antibiotics including antifungals (fluconazole) were used routinely and *n*-acetyl-cysteine was used in all cases of paracetamol poisoning.

OLTx was decided in the presence of laboratory tests indicating advanced liver dysfunction or rapidly increasing encephalopathy, according to the Kings College criteria [20], which we have found to be applicable in FHF patients in our center [16]. Patients with a history of repeated self-destructive behavior were not considered for OLTx but rather were treated with conservative medical treatment. ABO-compatible grafts were used in all cases. CVVH was continued until patients started diuresis and renal function tests improved. Postoperatively, patients were given routine immunosuppression with hydrocortisone, 200 mg/day, azathioprine, 2 mg/kg per day and cyclosporin, 10 mg/kg per day in two divided doses. Prophylactic antibiotics were continued for 48 h and prophylaxis for *Pneumocystis carinii* and for *Candidiasis* was given with cotrimoxazole and oral nystatin and amphotericin, respectively. Patients were routinely biopsied at 7 days postoperatively, and all patients were put on ranitidine during the first 3 months postoperatively.

The duration of intensive care stay, hospital stay and mechanical ventilation was determined to compare patients with normal renal function (group 1) and patients with acute renal failure (ARF; group 2). We excluded the presence of postrenal and prerenal disease as these patients had central pressure monitoring, were not volume-depleted, and had normal abdominal ultrasound scans. Follow-up at 3 and 12 months included observation of renal function as determined by serum urea and creatinine levels, surgical complications, immunosuppression levels of cyclosporin or FK 506, and differences in age and mortality between the two groups.

Table 1 Etiologic subgroups of patients with FHF ($n = 181$)

Cause	FHF No. (%)	Transplanted No. (%)
Drug-induced	124 (68.5)	7 (25.9)
Paracetamol overdose	115 (63.5)	3 (11.1)
Seronegative hepatitis	29 (16)	17 (62.9)
Fulminant hepatitis A	2 (1.1)	0
Fulminant hepatitis B	4 (2.2)	1 (3.7)
Fulminant Epstein-Barr	1 (0.6)	0
Acute fatty liver	5 (0.6)	0
Budd-Chiari syndrome	4 (2.2)	0
HELLP syndrome	2 (1.1)	0
Veno-occlusive disease	2 (1.1)	1 (3.7)
Acute Wilson's disease	1 (0.6)	1 (3.7)
Miliary tuberculosis	1 (0.6)	0
Posthepatectomy	1 (0.6)	0
Ischemic hepatitis	4 (2.2)	0
Acute lymphocytic lymphoma	1 (0.6)	0
Total	181	27

Table 2 Etiologic subgroups of FHF patients requiring OLTx ($n = 27$)

Cause	Normal renal function ($n = 13$) Group 1	Acute renal failure ($n = 14$) Group 2	Total ($n = 27$) No. (%)
Seronegative	9	8	17 (62.9)
Drug-induced	2	5	7 (25.9)
Paracetamol	1	2	3 (11.1)
Isoniazide	1	1	2 (7.4)
Halothane	0	1	1 (3.7)
Fluoxetine	0	1	1 (3.7)
Hepatitis B	1	0	1 (3.7)
Wilson's disease	1	0	1 (3.7)
Veno-occlusive disease	0	1	1 (3.7)

Results

Of the 181 patients with FHF, 27 (14.9 %) underwent OLTx (Table 1). These 27 patients (18 female, 9 male) had an average age of 43.5 years (range 19–65 years) and a wide range of etiologies. We observed that the main cause of liver failure was acute non-A, non-B, non-C hepatitis (seronegative hepatitis) in 17 of them (63 %), and that the second most common cause was drug-induced hepatitis in 7 (26 %); 3 patients had a paracetamol overdose and 4 idiosyncratic drug reactions (Table 2).

Seven of the 27 transplant recipients died. The most common cause of death was sepsis ($n = 4$) and the timing of death ranged from 3 to 62 days post-transplantation; there were two deaths within the first week (Table 3). *Enterococcus; species* and *Staphylococcus aureus* were isolated in blood cultures in one of the patients who died of sepsis, and in two patients *Aspergillus* was isolated. There was no evidence of preoperative infection in any of the patients. The seven patients who died had all presented with acute renal failure before transplantation, while there were no deaths among the group of patients who underwent transplantation with normal renal function (Table 4; Fig. 1). The overall survival was 67 % at 1 year.

We looked at the age of the patients transplanted for FHF to see if it affected mortality and found that five of the seven patients who died were more than 40 years old; a 16 % mortality rate was observed in the group below 40 years and a 33 % mortality rate in the group above 40 years (P = NS; Table 4). ARF presented in 14

Table 3 Mortality

Patient	Etiology	Cause of death	Time of death after OLTx (days)
1	Seronegative	Sepsis[a]	62
2	Veno-occlusive disease	Multiple organ failure	33
3	Hepatitis B	Sepsis[b]	33
4	Seronegative	Multiple organ failure/ARDS	17
5	Paracetamol overdose	Sepsis[c]	12
6	Seronegative	Cerebral oedema	3
7	Posthalothane	Sepsis[d]	7

Organisms cultured in blood:
[a] *Enterococcus species*, Staphylococcus aureus
[b] None
[c] *Aspergillus*
[d] *Aspergillus*

Table 4 Mortality according to renal function and age

	Alive		Dead		Total
	< 40 years	> 40 years	< 40 years	> 40 years	
Group 1 (normal renal function) $n = 13$	7	6	0	0	13
Group 2 (acute renal failure) $n = 14$	3	4	2	5	14
Total	10	10	2	5	27

of the 27 patients requiring OLTx. The most common form was oliguric renal failure in 11 of the 14. Comparing the two groups of transplant recipients, there was a higher incidence of drug-induced hepatic failure in those with ARF (group 2) 35.7 % compared to 15.3 % in those without ARF (group 1); yet, this difference was not significant. Otherwise, both groups were comparable with regard to age and etiology.

Duration in intensive care was significantly different in the two groups, with a median of 8 days for patients in group 1 and 17 days for those in group 2 (Table 5). Duration of mechanical ventilation was also significantly greater in group 2. The duration of hospital stay was a median of 21 days in group 1 compared to 29.5 days in group 2 (excluding two early deaths within the 1st week post-transplant); this difference was not statistically significant. Histological features in routine biopsy at day 7 post-transplant and surgical complications such as bleeding, bile leak, and retransplantation were not different between the two groups (Table 6).

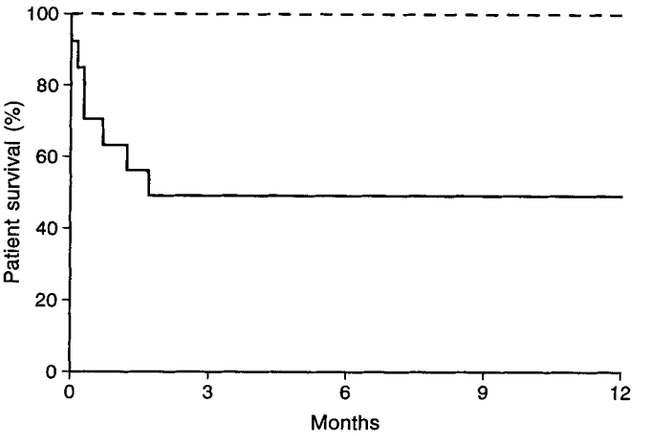

Fig. 1 Patient survival following OLTx for FHF in patients with *normal renal function* (- - - -) versus patients with *acute renal failure* (—)

Renal function at 3 and 12 months post-transplant, as determined by values of creatinine and urea, showed no significant difference between the two groups (median creatinine 111 μmol/l in group 1 vs 114 μmol/l in group 2; Table 5). Immunosuppression levels of cyclosporin and FK 506 were higher among patients in group 2 at 3 and 12 months post-transplant, although the difference was not statistically significant.

We also looked at the outcome of the 154 patients with FHF who did not undergo liver transplantation during this same period. Of these 154 patients, 82 had ARF and 72 had normal renal function. Forty-one of the 82 patients with ARF died (50 % mortality), and 15 of the 72 with normal renal failure died (20.8 % mortality).

Discussion

OLTx has become an established treatment for selected patients with FHF [14, 21, 22, 24–26]. One-year survival was 67 % for all of the FHF patients transplanted in this series, which is lower than the 88 % 1-year survival observed in elective OLTx at our center [13]. These figures are comparable to other centers where the survival rate for transplanted FHF patients varies from 40 to 75 % [8], which is lower than the survival rate for patients transplanted with chronic liver disease [11, 27].

For this retrospective analysis, we adopted a simple definiton of acute renal failure. Of course the pathogenesis of renal failure in this setting may be quite complex. Hepatorenal syndrome (HRS) may occur in the setting of both chronic liver disease and FHF. HRS has been defined as renal failure associated with oliguria and a rising serum creatinine, which occurs in the context of end-stage liver disease [9]. Some studies of HRS include

Table 5 Outcome according to presence of renal function pretransplantation

Events	Group 1 (Normal renal function) Median (range)	Group 2 (Acute renal failure) Median (range)	Mann-Whitney
Age	41.1 (19–65)	39.9 (19–60)	NS
Intensive care stay (days)	8 (4–26)	17 (3–36)	$P = 0.0114$
Intensive care stay (days) excluding deaths within the 1st week in group 2		17.5 (5–36)	$P = 0.0017$
Hospital stay (days)	21 (14–36)	27 (3–62)	NS
Hospital stay (days) excluding deaths within the 1st week in group 2		29.5 (12–62)	NS
Ventilation duration (days)	6 (3–13)	13 (3–33)	$P = 0.05$
Ventilation duration (days) excluding deaths within the 1st week in group 2		14.5 (4–33)	$P = 0.013$
Creatinine (mmol/l) at 3 months	111 (90–155)	114 (100–193)	NS
Creatinine (mmol/l) at 12 months	111 (85–600)	124 (105–140)	NS
Urea (mmol/l) at 3 months	7 (3.8–14.4)	8.75 (3.7–4.7)	NS
Urea (mmol/l) at 12 months	6.95 (5.8–42)	7.65 (6.6–9,4)	NS
Cyclosporin levels (ng/ml) at 3 months	216 (143–285)	178.5 (147–253)	NS
Cyclosporin levels (ng/ml) at 12 months	127 (94–304)	150 (121–244)	NS
FK 506 levels (ng/ml) at 3 months	6.7 (4.3–18.1)	18 (18)	NS
FK 506 levels (ng/ml) at 12 months	6.6 (4.8–8.4)	10.2 (10.2)	NS
Preoperative intensive care stay (days)	2.8 (0.5–4.0)	3.2 (0.7–5.0)	NS
Time of development of renal failure after onset of disease (days)	28.8 (1–160)	29.5 (1–120)	NS

Table 6 Surgical complications and histological features at routine biopsy on day 7

	Normal renal function ($n = 13$) Group 1	Acute renal failure ($n = 14$) Group 2	Total ($n = 27$)
Not biopsied	0	3[a]	3
No rejection	2	0	2
Mild rejection	5	3	8
Moderate rejection	2	4	6
Severe rejection	4	4	8
Bleeding	1	2	3
Bile leak	0	2	2
Retransplant[b]	2	0	2

[a] Three patients in group 2 were not biopsied. One had thrombocytopenic purpura and two died before day 7 post-transplantation
[b] One patient was retransplanted for massive hemorrhagic necrosis and the other for hepatic artery thrombosis

estimation of urinary sodium excretion. The majority of our patients were anuric and urinary sodium excretion could not be measured. For all patients, central venous lines were inserted, and it was observed that renal failure did not respond to adequate volume repletion. It seems likely that the majority of patients included in our study had HRS associated with FHF. Of course paracetamol poisoning is associated with liver and renal damage. In this setting, renal failure may be due to direct toxic effects of paracetamol. Paracetamol poisoning was classically associated with anuric renal failure. Under these circumstances it is not possible to distinguish renal failure due to direct paracetamol toxicity from renal failure that is consequent to the liver damage itself.

Renal failure may complicate acute and chronic liver disease. The development of renal failure usually reflects severe liver dysfunction and is associated with a very poor prognosis. Recovery of renal function is dependent upon recovery of hepatic function. In the setting of chronic liver disease, renal failure rarely resolves without liver transplantation. In the setting of FHF, recovery of renal function is also dependent upon recovery of liver function. This may occur with conservative management.

Renal dysfunction has been associated with diminished survival after transplantation in patients with primary biliary cirrhosis [15] as well as in other chronic liver diseases. In FHF patients there are series that have shown an increased incidence of renal failure in FHF with no adverse effect on survival [4]. In our center, the use of preoperative dialysis has been shown to be strongly associated with a poor outcome in these patients, which is consistent with reports from other series where renal failure has been known to be a deleterious clinical variable affecting survival in FHF patients [1, 5,

14]. We found in our study that 50 % of those patients with pretransplant renal failure died, whereas there were no deaths among patients with normal renal function. The development of renal failure indicates the severity of hepatic dysfunction and its higher association with a fatal outcome. Specifically for HRS, it is evident that OLTx can be a successful therapy [7]. Direct nephrotoxicty induced by medications, mainly paracetamol, could also explain the higher incidence of renal failure among the group of patients with drug-induced FHF.

Clinical outcome has been shown to correlate well with the United Network for Organ Sharing (UNOS) status at the time of transplantation [17, 18]. Our group of patients all had a status 3 or 4 – the greatest urgency for OLTx – as they were all hospitalized and most in intensive care. Their survival has been seen to be lower than status 1 patients with stable chronic liver diseases (100 % vs 54 %) [17], an observation supported by our experience.

All of the patients who died did so within 10 weeks of OLTx, and the most common cause of death was sepsis in four out of the seven deaths. There was no evidence of sepsis prior to liver transplantation in any of the patients. Bacterial sepsis is well known to present in FHF patients, which is why it is recommended that they have broad-spectrum antibiotic prophylaxis [3, 19]. Fungal infections are also common, particularly with *Candida* and *Aspergillus* species [4], and that is why in our unit there is a specific policy of adding fluconazole prophylactically in FHF patients. Aspergillosis is also known to occur in immunocompromised patients following OLTx; the development of sepsis is encouraged by the fact that these patients are mechanically ventilated and often have multiple central venous accesses and surgical drains.

Pretransplant renal failure was also a predictor of increased morbidity in our study. There have been series that show that patients with HRS prior to OLTx for chronic liver disease have increased morbidity post-transplantation [10, 12]. We observed a significant increase in mechanical ventilation and intensive care stay as well as a prolonged hospital stay. This has a direct effect on costs as these sicker patients require increased use of resources and a longer duration of intensive care and support.

There are studies that have shown no difference in survival in patients up to 70 years of age in chronic liver disease [2]. We looked at the age of these patients to see if it was a risk factor for increasing complications after OLTx, but there was not a statistically significant difference in mortality between patients above and below 40 years of age.

We observed that there was no significant difference in immunosuppression levels of cyclosporin and FK 506 between patients with ARF and those with normal renal function (P = NS), although cyclosporin levels were lower at 3 months in those patients with ARF, probably reflecting a lower dose administered to encourage renal recovery. This is standard practice in our center and has been shown to preserve renal function in other series [9, 10]. Despite pretransplant renal failure, no difference was encountered in the long-term renal function, assessed by serum urea and creatinine values 1 year after OLTx, and it appears that those who survive the acute episode of renal failure have good renal function 1 year after transplantation. This is something that has also been described in patients with HRS who have OLTx for chronic liver disease [10]. Nevertheless, we will continue to follow up these patients to see if there is deterioration in renal function after several years of immunosuppression, as there are reports of impairment after several years of OLTx in those patients who had ARF before transplantation [1].

In conclusion, survival of patients transplanted for FHF is inferior to that of patients transplanted for chronic liver disease. For patients with FHF undergoing transplantation, pretransplant renal failure strongly predicts poor outcome, although long-term outcome of renal function is good in those who survive. We have identified a subgroup of patients with normal renal function transplanted for FHF who have a good prognosis. With the current atmosphere of constrained resources, it is appropriate to focus our attention on those patients with the highest chance of survival and the lowest costs.

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