Nephrology Dialysis Transplantation

Original Article

The course of type 1 hepato-renal syndrome post liver transplantation

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Abstract

Background. Hepato-renal syndrome (HRS) is a functional form of renal failure that occurs in patients with end-stage liver disease. Previously considered fatal without liver transplantation, treatment with vasoconstrictors and albumin has been demonstrated to improve renal function in patients with type 1 HRS. Liver transplantation is still considered the definitive treatment for HRS. However, the renal recovery rate and those factors that predict recovery post orthotopic liver transplantation have not been determined.

Methods. We reviewed the hospital course of 28 patients who met the International Ascites Club criteria for type I HRS and who underwent orthotopic liver transplant. The patients' demographic and pre- and post-operative laboratory data were recorded; patients were followed for 4 months post-transplantation or until death.

Results. The MELD score of the patients was 30 ± 6. The mean duration of HRS prior to liver transplantation was 37 ± 27 days. HRS resolved in 16 patients (58%). The mean time to resolution of HRS was 21 ± 27 days, with a range of 4–110 days. Eight (50%) patients in whom the HRS resolved were undergoing pre-transplantation dialysis. The age of the recipients (49 ± 10 vs 56 ± 12; $P = 0.05$), the total bilirubin level on post-operative day 7 (6.0 ± 4.3 vs 10.1 ± 5.9 mg/dl; $P = 0.04$), alcoholic liver disease and the requirement for post-transplant dialysis were predictors of resolution of HRS by univariate analysis. Only alcoholic liver disease and post-transplant dialysis were independent (negative) predictors of resolution of HRS. Seven of the 12 (58%) patients who developed chronic renal insufficiency remained dialysis dependent. The pre-operative serum creatinine was non-significantly higher in the non-resolvers who remained dialysis dependent compared to those who did not require long-term dialysis (3.0 ± 1.0 vs 2.3 ± 0.4 mg/dl; $P = 0.1$) Four patients died; in three of these patients the HRS had resolved prior to their death.

Conclusion. HRS is not always cured by orthotopic liver transplant. Pre-transplantation dialysis or a long waiting period should not preclude transplantation in patients with HRS. HRS may not resolve in patients with alcoholic liver disease. We were unable to accurately define that group of patients with HRS who required long-term dialysis and could theoretically benefit from combined liver–kidney transplantation.

Keywords: cirrhosis; dialysis; hepato–renal syndrome; liver transplantation; renal failure

Renal failure is a common complication in patients with end-stage liver disease [1]. Pre-transplant renal dysfunction predicts a poorer outcome following liver transplantation [2]. In some cases, renal failure results from well-defined insults such as volume depletion, nephrotoxic drugs, sepsis or shock. However, in other cases renal failure in patients with cirrhosis occurs in the absence of well-defined insults and with normal renal histology. This disorder is known as the hepatorenal syndrome (HRS) [3]. HRS accounts for approximately 8% of cases of renal failure in patients with cirrhosis [3]. Gines and colleagues followed 234 non-azotemic patients with cirrhosis and ascites for 5 years; in this study 39% of the patients developed HRS [4]. The pathophysiological hallmark of HRS is vasoconstriction of the renal circulation. The mechanism of the vasoconstriction is incompletely understood; it may be multifactorial, involving disturbances in the circulatory function and activity of the systemic and renal vasoactive mechanisms [5,6]. In 1996, the International Ascites Club (IAC) established major and minor diagnostic criteria for the diagnosis of HRS [7]. HRS was further classified as type 1 and type 2 according to the rate of decline of renal function [3,7,8]. Type 1 was arbitrarily defined as a 100% increase in

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serum creatinine reaching a value of greater than 1.5 mg/dl in less than 2 weeks [3,7,8]. Patients who had a slower decline in renal function were deemed to have type 2 HRS.

Patients with type 1 HRS have a very poor prognosis compared to patients with type 2 HRS [9]. The median survival time for type 1 HRS has been reported to be 14 days [3,4,10,11]. The only effective medical therapy currently available for the management of HRS is the administration of vasoconstrictors together with volume expansion with a colloid (usually albumin). Volume expansion with colloids and vasopressin analogues (ornipressin and terlipressin), norepinephrine and somatostatin have been used with variable success [12–15].

Liver transplantation is considered the treatment of choice for patients with cirrhosis and type 1 HRS because it 'allows for both the liver disease and associated renal failure to be cured'. Surprisingly, while liver transplantation is considered the treatment of choice for patients with type 1 HRS, the percentage of patients whose renal function recovers, the time course of renal recovery and those factors which predict renal recovery have not been studied. These factors could influence decisions regarding the pre-operative management and timing of transplantation as well as the role of combined liver–kidney transplantation [16]. The purpose of this study was therefore to follow renal function post-orthotopic liver transplantation in patients with type 1 HRS and to determine those factors predictive of renal recovery.

Methods

This study was conducted in the 28 bed Liver Transplant ICU (LTICU) in Montefiore Hospital, University of Pittsburgh, Pittsburgh, PA, USA. Permission to perform this study was obtained from the University of Pittsburgh Institutional Review Board. The University of Pittsburgh Medical Center has a comprehensive electronic medical record system which archives patient clinical and laboratory data in a number of separate database systems. In addition, the LTICU has a separate database which records clinical and laboratory data on all patients admitted to the LTICU. Patients admitted to the LTICU between June 2001 and June 2004 who met the IAC criteria for the diagnosis of type 1 HRS and who underwent orthotopic liver transplantation were identified [7]. These criteria included: (i) a 100% increase in serum creatinine reaching a value of greater than 1.5 mg/dl in less than 2 weeks, (ii) absence of shock, ongoing bacterial infection, fluid losses, or concurrent treatment with nephrotoxic drugs, (iii) no sustained improvement in renal function with diuretic withdrawal and volume expansion, (iv) proteinuria of <500 mg/day and (v) no ultrasonographic evidence of obstructive uropathy or parenchymal disease. All patients with possible HRS were evaluated by a consultant nephrologist with expertise in the management of patients with liver disease.

Using an honest broker system, a de-identified data file was constructed. An honest broker system uses a third party (KG) not involved in the study to extract, collate and de-identify data files. The retrieved data included the duration of the HRS from the time the patients met the diagnostic criteria to the time of transplantation (in days), the need for pre-operative renal replacement therapy, history of diabetes mellitus and hypertension, the cause of liver failure, pre-operative laboratory data including liver function tests, blood urea nitrogen, serum creatinine and operative details (age of donor, cold ischaemic time, warm ischaemic time, number of red blood cells transfused during the procedure). The model for end-stage liver disease (MELD) equation was used to calculate pre-transplant disease severity as follows: $[0.957 \times \log_e$ (creatinine mg/dl) $+ 0.378 \times \log_e$(bilirubin mg/dl) and $1.12 \times \log_e$ (INR) $+ 0.643] \times 10$ [17]. The minimal values were set at 1.0 for calculation purposes. The maximal serum creatinine considered within the MELD score equation is 4.0 mg/dl. Post-operative data recorded included the need for and duration of renal replacement therapy, and daily serum creatinine and total bilirubin. In patients receiving haemodialysis, the immediate pre-dialysis creatinine level was used. HRS was considered to have resolved in patients who remained dialysis free with a serum creatinine of less than 1.5 mg/dl. All episodes of post-operative sepsis were recorded; the Society of Critical Care Medicine/American College of Chest Physicians criteria for sepsis were used [18]. Patients were followed for 4 months post-transplant or until death.

During the study period, patients undergoing liver transplantation (cadaveric, living related and non-heart beating donors) were treated with a steroid sparing regimen of immunosuppression. Patients received Campath (Alemtuzumab/ anti-CD 52 monoclonal antibody, Berlix Laboratories, Richmond CA) or thymoglobulin. Post-operative immunosuppression included oral tacrolimus which was delayed until post-operative day 2 or 3 in patients with HRS, with the dosage being adjusted to obtain a whole blood trough level of between 5–10 μg/ml. The tacrolimus level was very carefully monitored to ensure a trough level of ≤10 μg/dl in all patients until the HRS resolved. No patients received intravenous tacrolimus.

Statistical analysis

Summary statistics were compiled to allow a description of the patient population. Statistical analysis was done using NCSS 2004 (Kaysville, UT). Chi-squared analysis was used to compare categorical data. Continuous data were compared using Student's t-test. The Mann–Whitney U-test was used for data that failed tests of normality. Logistic regression analysis with forward variable selection was performed to determine those variables independently predictive of renal recovery. In the multivariate analysis, alcoholic liver disease was compared with non-alcoholic, liver disease as binary variables. Unless otherwise stated, all data are expressed as mean ± SD, with statistical significance declared for probability values of 0.05 or less.

Results

During the period under study, 28 patients with type 1 HRS underwent orthotopic liver transplantation. The mean MELD score of the cohort was 30 ± 6; their mean age was 51 ± 9 years and 19 (68%) were male. The mean

Table 1. Clinical and demographic characteristics of the patients with hepato-renal syndrome (HRS) grouped by post-transplant renal recovery

	HRS resolved $n = 16$	Persistent renal dysfunction $n = 12$
Age (years)	49 ± 10	56 ± 12*
Cause of liver disease		
alcohol	3 (18%)	8 (67%)**
hepatitis C	6 (37%)	3 (25%)
History of diabetes mellitus	5 (31%)	4 (33%)
History of hypertension	1 (6%)	4 (33%)
Duration of HRS prior to T/P (days)	38 ± 31	36 ± 22
Pre T/P albumin (g/dl)	2.9 ± 0.8	2.8 ± 0.6
Pre T/P creatinine (mg/dl)	3.1 ± 2.0	2.7 ± 0.9
Pre T/P INR	1.8 ± 0.5	2.0 ± 1.0
Pre T/P bilirubin (mg/dl)	13.3 ± 15.2	16.0 ± 18.1
Day 7 bilirubin (mg/dl)	6.0 ± 4.3	10.1 ± 5.9***
Pre MELD Score	31 ± 9	29 ± 8
Cold ischemia time (hours)	658 ± 296	671 ± 227
Warm ischemia time (minutes)	30 ± 9	34 ± 8
Age donor (years)	36 ± 15	49 ± 21
Intraoperative PRBC	14 ± 8	21 ± 20
Pre T/P dialysis	8 (50%)	5 (42%)
Post T/P dialysis	7 (43%)	11 (91%)*
Post T/P sepsis	5 (31%)	4 (33%)
LOS post T/P	34 ± 29	47 ± 33

HRS = hepato-renal syndrome; T/P = transplant; LOS = length of hospital stay; PRBC = packed red blood cells.
*$P = 0.05$; **$P = 0.02$; ***$P = 0.04$.

duration of HRS prior to liver transplantation was 37 ± 27 days. HRS resolved in 16 patients (58%). The clinical characteristics of the patients in whom HRS resolved compared to those who progressed to chronic renal insufficiency are listed in Table 1. The age of the recipients (49 ± 10 *vs* 56 ± 12; $P = 0.05$), the total bilirubin level on post-operative day 7 (6.0 ± 4.3 *vs* 10.1 ± 5.9 mg/dl; $P = 0.04$), alcoholic liver disease and the requirement for post-transplant dialysis were predictors of resolution of HRS by univariate analysis. The age of the donor (36 ± 15 *vs* 49 ± 21; $P = 0.07$) and the number of units of red cells transfused (14 ± 8 *vs* 21 ± 20; $P = 0.18$) tended to be lower in those patients in whom HRS resolved. Only alcoholic liver disease and post-transplant dialysis were independent (negative) predictors of resolution of HRS. The duration of the HRS prior to transplantation was 38 ± 31days (range 10–118) in those in whom HRS resolved and 36 ± 22 days (range 13–82) in those who progressed to chronic renal insufficiency. The mean time to resolution of HRS was 21 ± 27 days, with a range of 4–110 days. Only two patients demonstrated a rapid improvement in renal function with a dramatic increase in urine output post-transplant. The time to resolution of HRS was longer in those patients receiving pre-transplant dialysis; this was, however, not statistically significant (34 ± 36 *vs* 12 ± 12 days; $P = 0.1$). Seven of the 12 (58%) patients who developed chronic renal insufficiency remained dialysis dependent. The pre-operative serum creatinine was non-significantly higher in the non-resolvers who remained dialysis dependent compared

to those who did not require long-term dialysis (3.0 ± 1.0 mg/dl *vs* 2.3 ± 0.4 mg/dl; $P = 0.1$); the only variable which predicted long-term dialysis in the non-responders was the serum creatinine on post-operative day 7 (3.4 ± 0.9 μg/dl *vs* 1.6 ± 0.2 μg/dl; $P = 0.002$). Four patients died; in three of these patients the HRS had resolved prior to their death. All four of these patients required both pre-transplant and post-transplant dialysis. The mean age of the patients who died was 60 ± 5 years compared to 50 ± 9 years in the survivors ($P = 0.04$).

Discussion

A review of the literature would suggest that renal function improves in most patients with HRS post-orthotopic liver transplantation [1,3,6,8,19,20]. This belief is based on limited data. The main finding of our study is that type 1 HRS resolved in only 58% of patients post-transplantation. It could be argued that the 'low' resolution rate may be due to the fact that tacrolimus was used for immunosuppression, and that patients with HRS may be more susceptible to the nephrotoxicity of this agent. We think this to be unlikely, as initiation of tacrolimus was delayed, the blood levels were scrupulously monitored to limit the risk of nephrotoxicity and no patients received the drug intravenously. The requirement for pre-operative dialysis and a long waiting period prior to transplantation did not preclude renal recovery. It is generally believed that renal function improves immediately following transplantation; this pattern was observed in only two patients. The mean time to resolution of HRS was 21 ± 27 days, with a range of 4–110 days. While the reported median survival of patients with type 1 HRS is between 14–21 days [3,4,15], we have demonstrated that with aggressive medical management, patients can be supported for a prolonged time (up to 118 days) prior to successful transplantation. This experience is similar to that of Capling and Bastani, who reported a mean survival time of 236 days of four patients with type 1 HRS who underwent long-term haemodialysis [21].

Alcoholic liver disease independently predicted the failure of HRS to resolve after transplantation. The explanation for this observation is not entirely clear. Watt and colleagues reported that patients with alcohol-induced liver failure more often had HRS than did patients with other forms of liver failure (OR 45.1, CI 13.3–153.5, $P = 0.00001$) [9]. Increased levels of tumour necrosis factor-α (TNF-α) are found in patients with alcoholic liver disease [22,23]. TNF-α has been implicated as a cause of renal failure in patients with sepsis [24]. In addition, chronic alcohol abuse may increase the risk of renal failure by reducing prostaglandin synthesis [25,26], and by damaging the proximal convoluted tubule [27,28]. Further studies are required to confirm this observation.

Combined liver–kidney transplantation has been performed in patients with both hepatic and renal failure [29,30]. Data from the United Network for

Organ Sharing (UNOS) indicate that 12% of the combined liver–kidney transplants performed in the US (523 cases from 1988 to 1996) were in patients with HRS [31]. The 2- and 5-year overall survival rates for non-hepatorenal patients who received combined liver–kidney transplant were 79.8% and 69.2%, respectively, whereas HRS patients who received only liver transplant had 2- and 5-year survival rates of 73.8% and 67.1%, respectively (NS) [31]. In our study, we were unable to accurately define that group of patients who remained dialysis dependent post-transplant and would have potentially benefitted from combined liver–kidney transplant. However, the non-resolvers received organs from donors who tended to be older, they required more intra-operative blood transfusions and had slower hepatic recovery (higher bilirubin on day 7). This suggests that 'marginal' liver should not be used in patients with HRS.

A number of studies have evaluated renal function in patients undergoing orthotopic liver transplant. Gonwa et al. reviewed the post-operative course of renal function in 294 patients undergoing orthotopic liver transplant [19]. In this study, all patients received cyclosporin as part of the immunosuppressive protocol. HRS was defined by an increasing serum creatinine and a fractional sodium excretion (FeNa) of <0.1% in patients with end-stage liver disease. This study did not use the IAC criteria for HRS and did not distinguish between type 1 and type 2 HRS [3,7,8]. Thirty-one (10.5%) patients were considered to have HRS. In the non-HRS patients, glomerular filtration rate (GFR) declined from 97.1 ml/min at baseline to 56 ml/min at 6 weeks post-operation, 62 ml/min at 1 year and 58.3 ml/min at 2 years. In the patients with HRS, GFR increased from 19.9 ml/min at baseline to 32.5 ml/min at 6 weeks, 45.9 ml/min at 1 year and 37.9 ml/min at 2 years. Ten percent of HRS patients developed ESRD post-transplant compared to 0.8% of non-HRS patients ($P < 0.005$). The actuarial 1 and 2 year survival rates were similar in the non-HRS and HRS groups. In a follow-up study of 569 patients undergoing liver transplantation, these investigators reported a decreased actuarial 5-year survival in patients with HRS compared to patients without HRS (60 vs 68%, $P < 0.03$) [1].

Restuccia and colleagues compared the outcome of nine patients with HRS (three with type 1 HRS) who had been treated with vasopressin analogues before transplantation with a contemporary control group of patients ($n = 27$) without HRS [32]. The 3 year survival probability was similar between the two groups (100% HRS vs 83% control) and there were no significant differences between the two groups with respect to the incidence of renal impairment after transplantation, severe infections, acute rejection and LOS. Cassinello and coworkers studied the effect of orthotopic liver transplantation on vasoactive systems and renal function in 22 patients with cirrhosis [6]. In this study, there was a significant increase in the creatinine clearance and a significant fall in serum norepinephrine, plasma renin activity and endothelin-1

levels in both patients with and without HRS post-transplantation.

Although our study is limited by its retrospective design and small sample size, we demonstrated that at our centre, type 1 HRS resolved in 58% of patients post-orthotopic liver transplant. The mean time to resolution of renal failure was 21 days. Pre-transplantation dialysis or a long waiting period should not preclude transplantation in patients with HRS. HRS may not resolve in patients with alcoholic liver disease. HRS should not be considered an indication for combined liver–kidney transplantation.

Conflict of interest statement. None declared.

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