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Management of hepatorenal syndrome

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Abbreviations:
HRS, hepatorenal syndrome
MARS, Molecular absorbent recirculating system
MRI, magnetic resonance imaging
NSF, nephrogenic systemic fibrosis
TIPS, transjugular intrahepatic portosystemic shunt
TNFalpha, tumour necrosis factor alpha

ABSTRACT

Hepatorenal syndrome is a form of acute or sub-acute renal failure which develops in patients with chronic liver disease. In contrast to other forms of acute renal failure it may be reversible using pharmacological agents. The pathogenesis involves splanchnic vasodilatation and intense renal vasoconstriction. Increasing intravascular volume and prolonged treatment with vasoconstrictor drugs reverses renal failure in a significant proportion of patients. Agents currently used include the vasopressin analogues terlipressin and the alpha$_1$-adrenoceptor agonist midodrine. The somatostatin analogue octreotide has been used in combination therapy but is ineffective as monotherapy. Intravenous albumin is an important adjunctive treatment both in the prevention and treatment of hepatorenal syndrome. Increasing intravascular volume using TIPS (transjugular intrahepatic stent shunt) is effective in some patients and may be useful in maintaining patients who have initially responded to pharmacological therapy. Despite improvements in survival, long term prognosis is still poor and generally depends on the degree of reversibility of the underlying liver disease or access to liver transplantation.

Contents

1. Hepatorenal syndrome: clinical features and pathophysiology

Hepatorenal syndrome (HRS) is a functional renal failure which occurs in patients with advanced chronic liver disease. In general it occurs in patients with hepatic cirrhosis and ascites and may be precipitated by gastrointestinal bleeding, medication or infection (Cardenas et al., 2001; Terra et al., 2006; Fasolato et al., 2007). It is a functional, potentially reversible, form of renal failure which is caused by intense arterial vasoconstriction. In this condition, kidney histology is normal. Renal tubular function and the ability to concentrate urine are maintained. In patients with cirrhosis complicated by ascites, approximately 18% will develop hepatorenal syndrome at 1 year and 39% at 5 years (Gines et al., 1993). Infection is an important precipitant and approximately 28% of patients with spontaneous bacterial peritonitis will develop hepatorenal syndrome despite appropriate treatment with non-nephrotoxic antibiotics (Fasolato et al., 2007).

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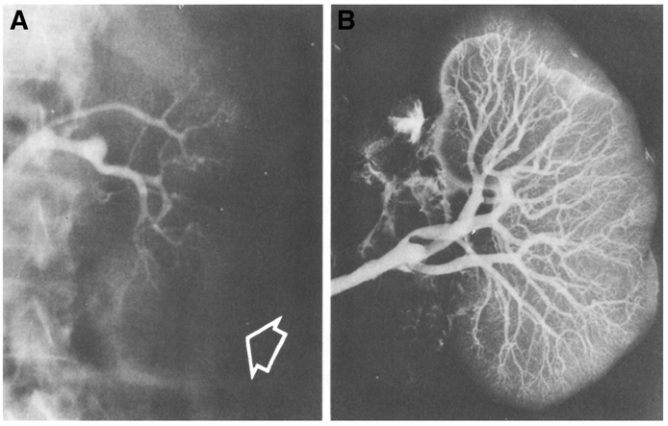

Fig. 1. Panel **A**. Angiogram in a patient with cirrhosis and hepatorenal syndrome demonstrating severe vasoconstriction and poor arterial filling. Panel **B**: Post-mortem angiogram in the same kidney demonstrating the intact renal vasculature. Reproduced from Epstein et al. (1970) by permission of Elsevier Limited.

Hepatorenal syndrome appears to be due to severe renal vasoconstriction, presumably reflex in response to splanchnic dilatation (Fig. 1). There is increased sympathoadrenal activation, reduced cortical blood flow, reduced renal perfusion pressure and increased interstitial pressure (Moller & Henriksen, 2004). The haemodynamic abnormalities are believed to be a result of peripheral arterial vasodilation, which occurs particularly in the splanchnic circulation and is associated with a reduction in central blood volume (Schrier et al., 1988; Moller et al., 2003) (Fig. 2). This causes functional hypovolaemia with reflex increased secretion of vasoconstrictor hormones including renin, angiotensin, anti-diuretic hormone, catecholamines and endothelin and activation of the sympathetic nerves to the kidney (Solis-Herruzo et al., 1987). In addition there appears to be some evidence to support a direct hepatorenal reflex (Jalan et al., 1997).

Table 1
Criteria for the diagnosis of hepatorenal syndrome, adapted from the International Ascites Club criteria (Arroyo et al., 1996; Salerno et al., 2007a)

- Cirrhosis with ascites.
- Serum creatinine >133 μmol/l (1.5 mg/dL).
- No improvement of serum creatinine (decrease to a level of 133 μmol/l) after at least 2 days with diuretic withdrawal and volume expansion with albumin. The recommended dose of albumin is 1 g/kg of body weight per day up to a maximum of 100 g/day.
- Absence of shock.
- No current or recent treatment with nephrotoxic drugs.
- Absence of parenchymal kidney disease as indicated by proteinuria >500 mg/day, microhaematuria (>50 red blood cells per high power field) and/or abnormal renal ultrasonography.

Major criteria must be present. Minor criteria may provide supportive evidence but are not mandatory.

2. Diagnosis of hepatorenal syndrome

The diagnostic criteria for hepatorenal syndrome agreed by the International Ascites Club and recently revised are shown in Table 1 (Arroyo et al., 1996; Salerno et al., 2007a). Essentially the diagnosis is made in patients with chronic liver disease who develop renal failure in the absence of other causes of renal disease. Hypovolaemia must be excluded along with evidence of structural renal disease e.g. obstruction or significant proteinuria. Renal tubular function is usually maintained, at least in the early stages with intact sodium reabsorption and concentrating ability. One of the difficulties with the published definitions is that the exclusion criteria include shock, ongoing bacterial infection and the use of nephrotoxic drugs. In

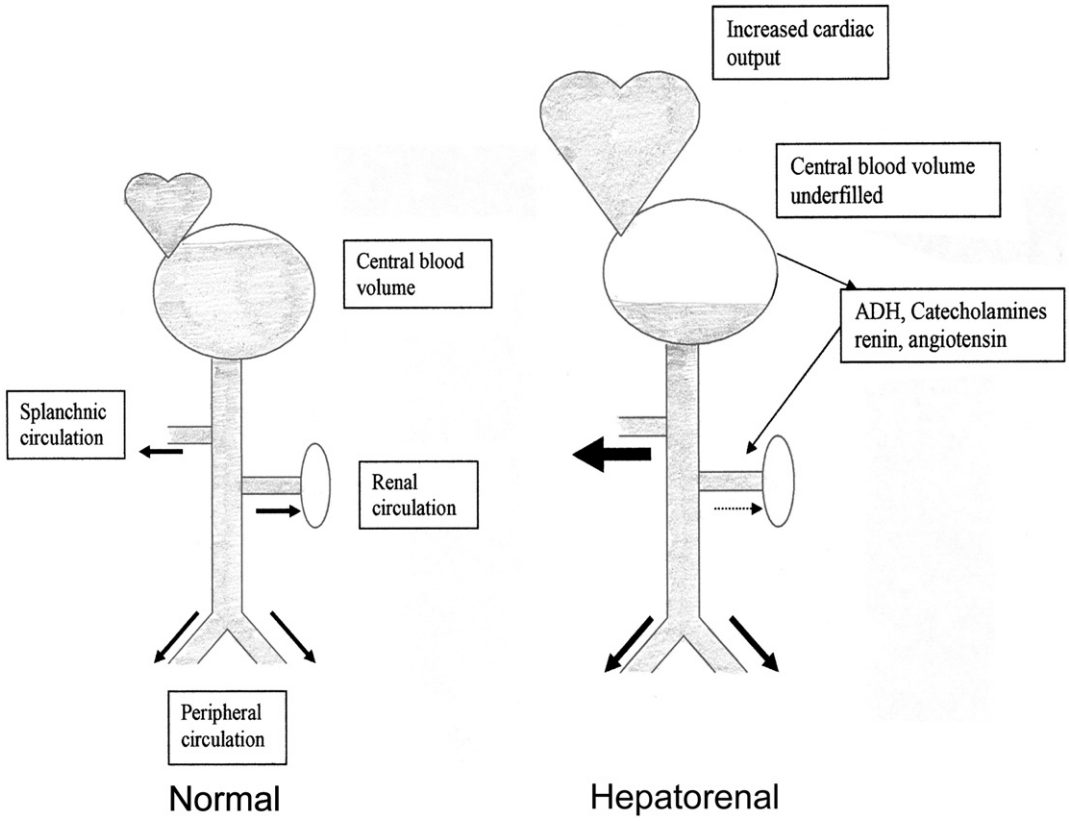

Fig. 2. Schematic representation of the arterial circulation. Size of arrows depicts relative blood flow. In patients with hepatorenal syndrome there is increased splanchnic arterial blood flow, underfilling of the central circulation and secondary renal vasoconstriction.

practice these are frequent precipitants of renal failure in cirrhotic patients, which is often progressive and has the characteristics of hepatorenal syndrome despite correction of the initiating events (Cardenas et al., 2001; Terra et al., 2006; Fasolato et al., 2007).

Hepatorenal syndrome is divided into two clinical types depending on the severity and speed of onset. Type 1 is defined as at least a 100% increase in the initial serum creatinine to a level greater than 226 μmol/l (25 mg/l), or a 50% reduction in the initial Glomerular Filtration Rate to a level lower than 20 ml/min within a period of 2 weeks. Type 2 hepatorenal syndrome comprises those patients with hepatorenal syndrome and a serum creatinine greater than 133 μmol/l who do not reach the criteria for type 1 HRS. The prognosis is much worse for patients with type 1 hepatorenal syndrome and this is the focus of most clinical research in this area. The studies discussed in this review refer to type I hepatorenal syndrome unless otherwise stated.

Hepatorenal syndrome should be distinguished from renal failure complicating fulminant hepatic failure. Fulminant liver failure is defined as hepatic encephalopathy developing within 8 weeks of the first manifestation of liver disease. The treatment of choice in this situation is early renal replacement therapy, usually with haemofiltration. If the liver recovers spontaneously, or if the patient receives a liver transplant, renal function almost invariably recovers. In contrast renal replacement therapy in hepatorenal syndrome complicating chronic liver disease is rarely associated with long term survival unless the patient receives a liver transplant within weeks (Mackle et al., 2006).

3. Prevention of hepatorenal syndrome

Prevention of hepatorenal syndrome is frequently neglected in clinical practice. The cornerstones of prevention are maintenance of hydration, prevention of/or early treatment of sepsis, avoidance of nephrotoxic medications and early intervention if there is evidence of deteriorating renal function. Cirrhotic patients with variceal bleeding, bacterial sepsis or acute alcoholic hepatitis are particularly at risk of developing renal dysfunction. Non-steroidal anti-inflammatory drugs, aminoglycosides and injudicious use of diuretics should be avoided, particularly in cirrhotic patients with ascites (McCormick et al., 1997). Intravenous albumin has been shown to prevent renal dysfunction in cirrhotic patients admitted with spontaneous bacterial peritonitis (Sort et al., 1999). In this study 1.5 g albumin/kg body weight was given at day 1 and day 3 and significantly reduced the incidence of renal impairment (33% vs 10%) and overall mortality (29% vs 10%) (Sort et al., 1999). In ascitic patients at high risk for spontaneous bacterial peritonitis, continuous prophylactic treatment with ofloxacin significantly reduced the incidence of hepatorenal syndrome and improved prognosis (Fernandez et al., 2007). The TNFalpha synthesis inhibitor pentoxifylline significantly reduced the incidence of hepatorenal syndrome in a controlled trial of patients admitted with severe acute alcoholic hepatitis (Akriviadis et al., 2000).

In patients with liver disease and renal insufficiency, gadolinium containing magnetic resonance imaging (MRI) contrast agents should be avoided. Use of these agents has been associated with the development of nephrogenic systemic fibrosis (NSF) (Peak and Sheller, 2007). This is a rare, severe, progressive, systemic fibrosing disorder which involves the skin and internal organs and can lead to disability and death.

4. Treatment of hepatorenal syndrome

Definite evidence of reversibility of the hepatorenal syndrome came from liver and kidney transplant studies from the 1960s and 1970s (Koppel et al., 1969; Iwatsuki et al., 1973). Clinical physiological studies in the 1960s suggested that systemic vasoconstrictors may reverse some of the features associated with renal dysfunction in cirrhosis (Cohn et al., 1968). Subsequent studies showed that increasing effective blood volume and administration of vasoconstrictors infusions reversed sodium retention and normalised plasma aldosterone levels in patients with cirrhosis and ascites. This was accomplished by a combination of intravenous water loading, the manoeuvre of head-out water immersion and intravenous infusion of norepinephrine (noradrenaline) (Nicholls et al., 1986). Head-out water immersion involves the patient being immersed up to the neck in a water bath for up to 5 h. This results in significant, short-term, improvements in renal function in cirrhotic patients with ascites but is clearly not practical as a routine treatment.

Vasopressin and its analogues were found to be more effective vasoconstrictors of the mesenteric than the renal circulation, a property which may be useful in hepatorenal syndrome by favouring renal blood flow (Schmid et al., 1974; Heyndrickz et al., 1976). Subsequently Guevara et al. (1998a) demonstrated that prolonged treatment with the vasopressin analogue ornipressin, combined with plasma volume expansion with albumin, returned renal function to normal in many patients. It is important to note that treatment for 7–14 days was required to achieve these results. Ornipressin was given as a continuous infusion increasing from 2 IU/h on day 1 to 6 IU/h on day 3. Intravenous albumin (albumin 20%) was given at a dose of 1 g/kg body weight on day 1 and then daily at 20–60 g/day depending on pulmonary capillary wedge pressure. Pulmonary capillary wedge pressure is used as a measure of left atrial pressure which is dependent on degree of hydration (i.e. blood volume). Three patients were withdrawn because of ischaemic complication including colonic ischaemia, tongue ischaemia and asymptomatic ventricular tachycardia.

Subsequently, a number of studies have shown that the combination of intravenous albumin and another vasopressin analogue, low dose terlipressin (0.5–2 mg, 4–6 hourly intravenously), significantly improved renal function and probably prognosis (see Table 1). Terlipressin is a long acting analogue of vasopressin in which lysine is substituted for arginine at position 8 and the *N*-triglycl residue is cleaved by endothelial peptidases releasing the active drug (Fig. 3) (Kam et al., 2004). Three vasopressin receptor types have been described (V1-3). Terlipressin selectively acts on V1 which is found on vascular smooth muscle cells, causing vasoconstriction (Treschan & Peters, 2006). Two recent meta-analyses support the concept that terlipressin improves prognosis in patients with hepatorenal syndrome (Fabrizi et al., 2006; Gluud et al., 2006). As a result terlipressin is now widely used for the treatment of type 1 hepatorenal syndrome although more definitive studies are still needed (Moreau & Lebrec, 2006). While terlipressin is reported to be safer than ornipressin, serious ischaemic complications or hyponatraemia may occur and limit treatment (Donnellan et al., 2007).

An alternative approach to glypressin has been to use alpha-adrenoceptor agonists such as midodrine. One study used a combination of the somatostatin analogue octreotide with midodrine and intravenous albumin (Angeli et al., 1999). Twenty days of treatment significantly improved renal function. Survival was also improved compared to historical controls treated with low dose dopamine and intravenous albumin. In a recent retrospective study, 60 patients with type 1 HRS treated with octreotide and midodrine were compared with 21 contemporary untreated patients. The treated patients had improved renal function and survival at 30 days (57% vs 29%) (Esrailian et al., 2007). Midodrine has advantages in that it is an oral medication. One study used intravenous albumin, intravenous noradrenaline and furosemide. The dose of noradrenaline was titrated to increase mean blood pressure by at least 10 mmHg (0.5–3 mg/h intravenously). Reversal of type 1 HRS was noted in 10/12 patients after a median of 7 days treatment (Duvoux et al., 2002).

Volume repletion with intravenous albumin has been used in most studies. In a prospective non-randomized study, Ortega et al. (2002) looked at the outcome in 13 patients who received intravenous albumin and terlipressin compared to 8 patients who received terlipressin alone. Seventy seven percent of the albumin group had a complete response compared to 25% of those who received

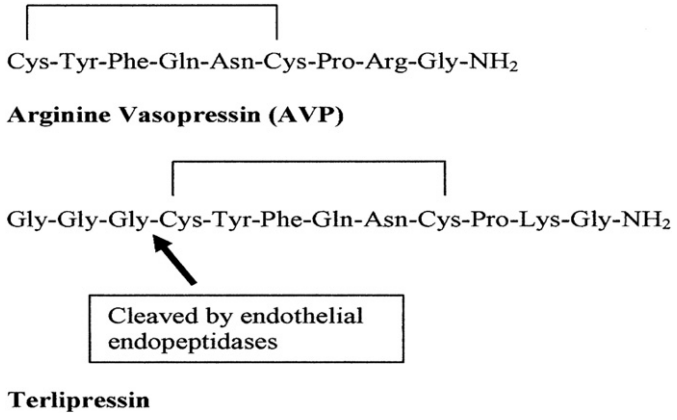

Fig. 3. Structure of arginine vasopressin and its long acting analogue terlipressin (glypressin).

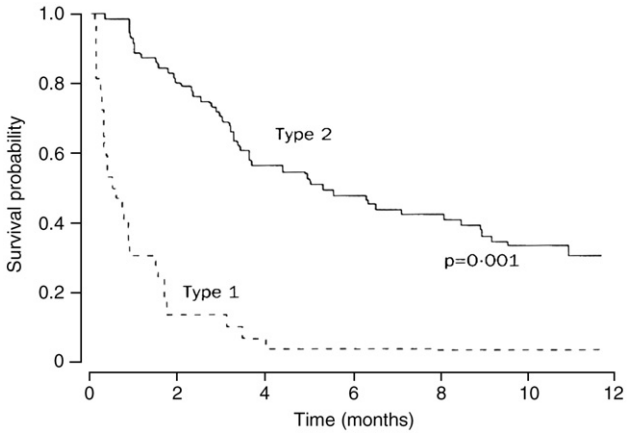

Fig. 5. Survival probability after the diagnosis of type 1 or type 2 hepatorenal syndrome in cirrhotic patients. Reprinted from Gines et al. (2003) with permission from Elsevier.

terlipressin alone. In a retrospective multicenter study, Moreau et al. (2005) found that patients with hepatorenal syndrome who had received intravenous albumin following paracentesis (removal of peritoneal fluid build-up caused by ascites) in the pre-HRS period had improved survival compared to those who received another plasma expander.

Most clinical studies have reported results employing vasoconstrictors in type 1 hepatorenal syndrome. Alessandria et al. (2005) reported results on 11 patients with type 2 hepatorenal syndrome. Renal function improved in 8/11 patients. Nine patients were subsequently treated with TIPS (transjugular intrahepatic portosystemic shunt, see below) and renal function improved significantly in all those who had responded to terlipressin.

A number of therapies appear to be ineffective in hepatorenal syndrome. These include intravenous albumin combined with dopamine (Angeli et al., 1999), intravenous albumin and octreotide (Pomier-Layrargues et al., 2003), and octreotide monotherapy (Kiser et al., 2005). In ascitic patients without renal failure midodrine combined with octreotide had no haemodynamic benefits compared to midodrine alone (Kalambokis et al., 2005). The non-selective endothelin receptor is ineffective in patients with type 2 HRS. Its use was complicated by systemic hypertension and worsening renal function (Wong et al., 2008).

5. Hepatorenal syndrome and TIPS

TIPS (transjugular intrahepatic portosystemic shunt) is a method of creating a portal systemic venous shunt in order to reduce portal venous pressure (Fig. 4). As a result of shunting, TIPS also increases central blood volume. The shunt is created using interventional radiological techniques and a metal stent inserted to maintain patency. TIPS is now frequently used for the treatment of refractory ascites and appears to improve transplant free survival (Salerno et al., 2007b). Four randomized controlled trials have now been performed suggesting that TIPS is superior to large volume paracentesis in controlling ascites. Resistant ascites is often a forerunner of hepatorenal syndrome suggesting that it would be reasonable to assess TIPS in this context, but as yet few studies have been published (Guevara et al., 1998b; Brensing et al., 2000; Wong et al., 2004). Brensing et al. (2000) treated thirty-one non-transplantable patients (14 type 1 and 17 type 2), and found that renal function improved following TIPS. One and two year survival figures were 20% and 20% for type 1 and 70% and 45% for type 2. An important caveat is that accelerated liver failure is

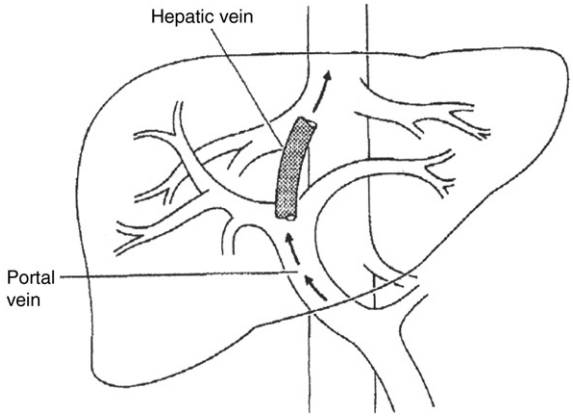

Fig. 4. Diagrammatic representation of a TIPS (transjugular intrahepatic portosystemic shunt) linking the portal and hepatic veins. It reduces portal venous pressure and increases venous return and central blood volume. The shaded structure represents a metal stent inserted to maintain shunt patency Reproduced from McCormick et al. (1994) by permission of the publisher Wiley–Blackwell Ltd.

Table 2
Results of pharmacological treatment of hepatorenal syndrome

	No (type 1)	Alcoholic	Response	Recurrence	Median survival
Pre-vasoconstrictor therapy					
Gines et al., 1993, 2003[a]	56 (56)	68%	n/a	n/a	14 days
Ornipressin (prolonged therapy)					
Guevara et al., 1998a	8 (8)	38%	100%[b]	50%	60 days
Gulberg et al., 1999	7 (7)	57%	57%	50%	90 days
Terlipressin					
Uriz et al., 2005	9 (6)	67%[c]	77%	0%	39 days
Mulkay et al., 2001	12	75%	92%	55%	42 days
Moreau et al., 2005	91	89%	58%		43 days
Colle et al., 2002	18	70%	61%	64%	24 days
Halimi et al., 2002	18	100%	72%		
Ortega et al., 2002	16[a]	43%	50%	12%	40 days
Solanki et al., 2003	12	33%	42%		8.5 days
Alpha-agonists					
Duvoux et al., 2002	12	67%	83%	0%	60 days
Angeli et al., 1999	5	40%	100%	0%	
Esrailian et al., 2007	60	45%	40%	n/a	71% (30 days)
Octreotide					
Pomier-Layrargues et al., 2003	14	70%	10%		
Kiser et al., 2005	8	n/a	12.5%	n/a	13 days approx.[d]

n/a = not available.
[a] patients with type 1 HRS.
[b] 50% withdrawn early due to side effects.
[c] 4 alcohol, 2 alcohol + Hepatitis C Virus.
[d] = mean survival of non-responders.

one of the most frequent causes of death following TIPS. It appears that excluding patients with high bilirubin (>51 μmol/l or 3 mg/dL) may reduce the likelihood of liver failure (Gerbes & Gulberg, 2005). TIPS may have a role in maintaining patients who initially respond to vasoconstrictor treatment. Wong et al. (2004) treated 14 ascitic cirrhotic patients with type 1 HRS using a combination of midodrine, octreotide and albumin. Medical therapy for 14 days improved renal function in 10/14 patients with mean serum creatinine significantly falling from a mean of 233 μmol/l to a mean of 112 μmol/l. Five responders were then treated with TIPS with further improvement in renal function (mean glomerular filtration rate: 96 ± 20 ml/min at 12 months).

6. Molecular absorbent recirculating system therapy (MARS)

The Molecular absorbent recirculating system (MARS) may be useful in some patients with hepatorenal syndrome. One small randomized trial has been performed. The authors chose patients with severe underlying liver disease (Child Pugh class C—mean score 12.4 and serum bilirubin > 15 mg/dL) (Mitzner et al., 2000). Thirteen patients were randomized—8 treated with MARS and 5 controls. A mean of 5 treatments were given. Mortality was 100% in the control arm by day 7 compared to 62.5% in the MARS group.

7. Hepatorenal syndrome and liver transplantation

Given the poor long term prognosis of patients with hepatorenal syndrome, liver transplantation offers the best prospect of long term survival. Renal function is known to improve in most patients following liver transplantation (Gonwa et al., 1991). However many patients do not survive long enough to receive a transplant. With improving medical therapy increasing numbers of patients with hepatorenal syndrome are surviving on the waiting list. In general survival rates at 1, 3 and 5 years post-transplant are 10% lower in patients with HRS at the time of liver transplant, compared to patients with normal renal function (Ruiz et al., 2007). An important clinical question concerns the prognosis of patients with HRS treated with vasoconstrictors who subsequently undergo liver transplant. Restuccia et al. (2004) studied 9 patients in this situation and compared them to 27 matched patients without renal dysfunction. Length of Intensive Care Unit (ICU) stay, hospital stay and incidence of renal dysfunction were similar for the two groups. Three year survival was 100% in the HRS group and 83% in controls.

Surprisingly, renal function does not always recover following successful liver transplantation. Marik et al. (2006) studied 28 patients with hepatorenal syndrome prior to liver transplantation. HRS resolved in 16, 12 had long term renal insufficiency and 7 remained dialysis dependent (Marik et al., 2006). In another study the duration of renal dysfunction pre-transplant was the best predictor of chronic renal dysfunction post-transplant (Campbell et al., 2005). If the duration of dialysis pre-transplant was less than 30 days only 8% of patients still required haemodialysis 8 weeks after transplant (Ruiz et al., 2006). The long term outcome is particularly poor for patients who continue to require dialysis >60 days post liver transplant (Ruiz et al., 2007). Another question is whether patients with end stage liver failure and established renal failure should be treated with single liver transplant or combined liver and kidney transplant. In a large retrospective study which included 22 patients with HRS, combined liver/kidney transplantation did not confer a survival advantage over liver transplant alone (1 year patient survival 72% vs 66% p p = 0.88) (Ruiz et al., 2006).

8. Prognosis of hepatorenal syndrome

Hepatorenal syndrome is associated with a very poor prognosis (Gines et al., 1993, 2003). Before the advent of newer therapies the median survival for patients with type 1 HRS was 1.7 weeks and 90% were dead within 10 weeks of diagnosis (Fig. 5). In contrast, type 2 HRS has a median survival of approximately 6 months and a 1 year survival of about 30%. The past 15 years have witnessed major advances in the prevention and treatment of hepatorenal syndrome. Although randomised controlled trials are lacking it appears that treatment has improved short-term prognosis. Nevertheless for most patients with type 1 hepatorenal syndrome prognosis is still very poor (Table 2). Long term prognosis is still determined by the underlying liver disease, where progress in improving prognosis has unfortunately been slow (Roberts et al., 2005).

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