Hepatorenal Syndrome

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April 7, 2008

Introduction

The hepatorenal syndrome (HRS) is one of the most feared complications of end-stage liver disease, and is seen mainly in patients with advanced cirrhosis and ascites. It is best described as a functional renal failure, resulting from marked circulatory dysfunction seen in the advanced stages of cirrhosis. The hallmark of this syndrome is severe renal vasoconstriction. While the syndrome was first described in detain in the 1950s, an association between liver disease and renal failure has been known for more than a century[1]. The functional nature of this syndrome was established when the kidneys of these patients were successfully transplanted to other patients with chronic renal failure, and that renal failure was also reversible after liver transplantation[2]. Until recently, liver transplantation was the only viable option for treatment. However, the limits of organ availability for transplant have led to high mortality rates for this syndrome. More recently, the pathophysiology underlying HRS has been defined. This has paved the way for newer treatment modalities, which show promise in treating a syndrome that maintains a high mortality rate without liver transplantation.

Clinical and Laboratory Manifestations

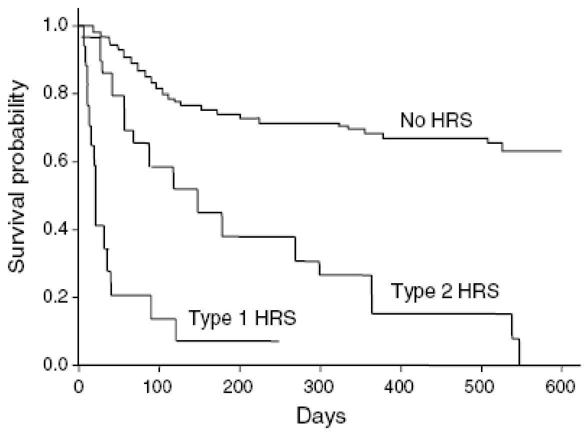
There are two distinct types of HRS[3]. Type 1 HRS is characterized by a rapid and progressive impairment of renal function. This is defined as a doubling of the serum creatinine to a level higher than 2.5mg/dL or a 50% reduction of the initial 24-hour creatinine clearance to a level less than 20mL/min in less than 2 weeks. In contrast to type 1 HRS, type 2 is characterized by a slower and steadier decrease in renal function. This manifests as a rise in serum creatinine to a level greater than 1.5mg/dL. The main clinical consequence of type 2 HRS is the development of diuretic-resistant ascites[4].

There is no clinical or laboratory picture specific for HRS, except as defined above. These patients have many of the features present with advanced liver disease, in addition to renal dysfunction. These patients may have underlying ascites which is refractory to diuretic therapy. The ascites may be complicated by the development of spontaneous bacterial peritonitis. Also present is arterial hypotension. In addition, they may present with hyperbilirubinemia, encephalopathy, and coagulopathy from elevated prothrombin time and thrombocytopenia. Marked oliguria is present, with less than 500cc of urine output per day. Also noted is extreme sodium conservation, with urinary sodium levels less than or equal to 10 mEq/L. Patients may also present with a dilutional hyponatremia, with serum sodium concentrations of less than 130 mEq/L.

Epidemiology

HRS is estimated to occur in 10% of patients hospitalized with cirrhosis and ascites[5]. In addition, the probability of developing HRS was shown to be 18% at 1 year and 39% at 5 years in the largest study to date looking at the epidemiology of HRS[5]. This study found sixteen of thirty-nine studied to have predictive value for the occurrence of hepatorenal syndrome. This list includes ascites, dilutional hyponatremia, high plasma renin activity, low glomerular filtration rate, and elevated levels of serum BUN and creatinine.

Interestingly, neither the degree of liver failure nor the Child-Pugh classification correlated with the risk of developing HRS. Certain clinical settings predispose to the development of hepatorenal syndrome. Approximately 20% of patients with spontaneous bacterial peritonitis (SBP) will develop type 1 HRS, despite rapid resolution of the infection with antibiotics. Fifteen percent of patients undergoing large-volume paracentesis (> 5L removed) without albumin replacement will also develop type 1 HRS.



HRS carries the worst prognosis of all the complications of cirrhosis[3]. Without treatment, the median survival time of type 1 HRS is less than 2 weeks. Type 2 HRS carries a slightly better prognosis, with a median survival time of about 6 months.

Diagnosis

HRS is a diagnosis of exclusion. There is no single laboratory or clinical marker that will establish the diagnosis. The first step in the diagnosis is the demonstration of a reduced GFR[3]. This is usually manifest as a rise in serum creatinine or a reduction in creatinine clearance, as measured in a 24-hour urine collection. However, these measurements can be fraught with error. It is common for cirrhotics with advanced liver disease to have low muscle mass, and thus low endogenous production of creatinine. These patients can have significant reductions of GFR in the presence of normal serum creatinine values. Similarly, measurements of blood urea nitrogen (BUN) may be of limited clinical utility. Advanced liver dysfunction may lead to deficiencies in the urea cycle. This in turn may lead to lower than expected values for BUN, despite the presence of significant kidney dysfunction.

Other causes of renal failure must be ruled out to make the diagnosis. Patients may have pre-renal failure from volume losses caused by hemorrhage, diuretic use, vomiting, or diarrhea. Renal function in these settings rapidly improves with volume expansion and, if needed, diuretic withdrawal. Nephrotoxic drugs such as non-steroidal anti-inflammatory agents and certain antibiotics, along with radiocontrast agents, may precipitate renal failure. Obstructive uropathy should be investigated with ultrasound imaging. Glomerulonephritis, most commonly from untreated viral hepatitis in these patients, may also be present. The presence of shock before the onset of renal failure usually points toward acute tubular necrosis as the underlying etiology[6].

Due to the lack of specific testing for HRS, the International Ascites Club (IAC) has established specific diagnostic criteria[7]. These include both major and minor criteria. A reduced GFR, as demonstrated by a serum creatinine greater than 1.5mg/dL, is essential for diagnosis. Volume depletion, ongoing bacterial infection, shock, and use of nephrotoxic drugs must also be excluded. There must also be no improvement in renal function after diuretic withdrawal and/or volume repletion with 1.5 liters of saline. Finally, proteinuria (>500mg/day) or sonographic evidence of obstruction or parenchymal renal disease exclude the diagnosis of HRS.

TABLE 2. International Ascites Club's Diagnostic Criteria of Hepatorenal Syndrome

Major Criteria
Chronic or acute liver disease with advanced hepatic failure and portal hypertension.
Low glomerular filtration rate, as indicated by serum creatinine of >1.5 mg/dL or 24-h creatinine clearance <40 mL/min.
Absence of shock, ongoing bacterial infection, and current or recent treatment with nephrotoxic drugs. Absence of gastrointestinal fluid losses (repeated vomiting or intense diarrhea) or renal fluid losses (weight loss >500 g/d for several days in patients with ascites without peripheral edema or 1,000 g/d in patients with peripheral edema).
No sustained improvement in renal function (decrease in serum creatinine to 1.5 mg/dL or less or increase in creatinine clearance to 40 mL/min or more) following diuretic withdrawal and expansion of plasma volume with 1.5 L of isotonic saline.
Proteinuria <500 mg/dL and no ultrasonographic evidence of obstructive uropathy or parenchymal renal disease.
Additional Criteria
Urine volume <500 mL/d.
Urine sodium <10 mEq/L.
Urine osmolality greater than plasma osmolality.
Urine red blood cells <50 per high power field.
Serum sodium concentration <130 mEq/L.

Currently, there are proposals to revise and update these criteria[4]. Renal failure in the setting of ongoing bacterial infection, but in the absence of septic shock, is now considered HRS. This criteria change will allow treatment for HRS to begin before waiting for complete recovery from infection. In addition, plasma expansion should be performed with albumin rather than saline. While there is no conclusive data to support the use of albumin over saline for volume expansion, there appears to be a consensus among experts favoring its use in diagnosis of HRS. This proposal may stem from the use of albumin in the treatment of spontaneous bacterial peritonitis and after large-volume paracentesis. There is data to support the use of albumin in these clinical settings to prevent the development of circulatory dysfunction and HRS[8,9]. Finally, the minor diagnostic criteria were removed as they were deemed non-essential in diagnosis.

Pathogenesis

The pathophysiologic hallmark of HRS is severe vasoconstriction of the renal circulation[10]. The underlying mechanisms are complex, and have only recently been elucidated. Intense renal vasoconstriction is seen as the end-result of decreased effective arterial volume and activation of vasoconstrictor systems, despite the presence of ascites and portal hypertension. Recently, it has been proposed that a coexisting cardiac dysfunction may contribute to the development of HRS[11].

Splanchnic Arteriolar Vasodilatation

The presence of cirrhosis and portal hypertension is associated with the development of arterial vasodilatation, particularly in the splanchnic vascular beds[6]. Circulating vasodilators responsible for vasodilatation include nitric oxide (NO), glucagons, and vasoactive intestinal polypeptide (VIP), among others[11]. Recently, experimental evidence has shown that mild increases in portal pressures lead to the upregulation of nitric oxide synthase[12]. Along with overproduction, these vasodilators escape hepatic degradation due to portosystemic collateralization and advanced liver dysfunction inherent in cirrhotics[11]. The end result is the development of arterial underfilling and a decrease in effective arterial volume (EAV), which manifests clinically as hypotension. This in turn leads to the activation of numerous vasoconstrictor systems[11], including the rennin-angiotensin-aldosterone system (RAAS), the sympathetic nervous system (SNS), and anti-diuretic hormone (ADH). Despite their activation, the splanchnic vasculature has been shown to display decreased responsiveness to these vasoconstrictors[13]. Arterial pressure is maintained by the actions of vasoconstrictors on the extra-splanchnic circulation, particularly the renal vasculature. These changes may occur progressively over time, or may be accelerated by the development of several complications of ascites, including spontaneous bacterial peritonitis. Ultimately, it is the constriction of the renal vascular beds which is responsible for the manifestations of HRS.

Hyperdynamic Circulation

The prevailing theory on cardiac function in cirrhotics is that of a hyperdynamic circulation, with increased cardiac output. The resulting arterial hypotension from splanchnic vasodilatation causes a decrease in systemic vascular resistance (SVR). This decrease in SVR stimulates baroreceptors in the atria and carotid bifurcation. The result is activation of the SNS, with increases in heart rate and contractility. Cardiac output subsequently increases. Despite this theory, the few studies that have investigated the hemodynamics in patients with HRS have actually found cardiac output to be significantly reduced compared to non-HRS patients[14-16]. Some investigators thus postulate that cardiac dysfunction is present in patients with HRS, and may contribute to its underlying pathophysiology.

Cirrhotic Cardiomyopathy

While the concept of cardiac dysfunction in cirrhotics was first proposed over forty years ago[14], it is only recently that studies measuring hemodynamics specifically in patients with HRS have validated this concept. One such study conducted by Ruiz-del-Arbol, et al. was a longitudinal in a large series of non-azotemic cirrhotic patients with ascites[15]. The study measured cardiovascular hemodynamics via Swan-Ganz catheterization, as well as plasma levels of vasoactive systems (plasma renin activity, norepinephrine, and aldosterone). Repeat measurements were made in 27 of the 66 patients in the study who developed HRS during the study period. The investigators observed a significant difference in baseline cardiac output between the HRS and non-HRS groups (6.0 ± 1.2 L/min vs. 7.2 ± 1.8 L/min, p <0.01). After the development of HRS, this group of patients exhibited an even further decline in cardiac output (5.4 ± 1.8 L/min, p <0.005). The same results were observed with several other variables, including mean arterial pressure, plasma renin activity, plasma aldosterone levels, and plasma norepinephrine levels. Interestingly, there was no significant difference in SVR between both groups at baseline or after the development of HRS. Right atrial and pulmonary capillary wedge pressures were not significantly different between the HRS and non-HRS groups at baseline, but statistically significant differences were shown between groups after the development of HRS.

Table 1. Baseline Measurements in Patients Who Did Not Develop Hepatorenal Syndrome (Group A) and Baseline and Follow-up Measurements in Patients Who Presented With Hepatorenal Syndrome (Group B)

	Group A (n = 39)	Group B (n = 27)	
	Baseline Measurements	Baseline Measurements	Follow-up Measurements
Serum bilirubin (mg/dL)	2.7 ± 1.9	3.8 ± 3.9	4.3 ± 3.9
Serum albumin (g/L)	24 ± 4	24 ± 5	24 ± 4
Prothrombin index (%)	64 ± 14	59 ± 14	51 ± 13††††
Child-Turcotte-Pugh score (points)	9.7 ± 1.3	9.9 ± 1.3	10.8 ± 2.1†
MELD score (points)	13.7 ± 4.0	15.8 ± 4.6	25.7 ± 6.8††††
Serum creatinine (mg/dL)	0.85 ± 0.18	1.05 ± 0.26***	3.03 ± 1.49††††
Serum sodium (mmol/L)	134.5 ± 4.8	132.6 ± 4.6	127.0 ± 5.1††††
Urinary sodium (mmol/L)	17.4 ± 18.9	7.0 ± 6.1***	4.0 ± 4.5†
MAP (mmHg)	88 ± 9	83 ± 9*	75 ± 7††††
HR (bpm)	87 ± 15	85 ± 13	82 ± 14
RAP (mmHg)	6.7 ± 2.5	6.9 ± 2.6	5.7 ± 2.2†
PAP (mmHg)	15.2 ± 3.8	14.3 ± 4.3	12.8 ± 2.8††
PCWP (mmHg)	9.2 ± 3.2	9.2 ± 2.6	7.5 ± 2.6††††
CO (L/min)	7.2 ± 1.8	6.0 ± 1.2**	5.4 ± 1.5†††
SVR (dyne · s/cm^{-5})	962.0 ± 256.4	1,058.6 ± 265.6	1,096.1 ± 327.6
Stroke volume (mL/beat)	85.2 ± 17.0	73.2 ± 18.9*	65.3 ± 18.8†
Stroke work (gm-m)	91.3 ± 17.9	75.3 ± 22.9**	62.7 ± 21.3††††
Left ventricular stroke work (gm-m)	140.0 ± 32.6	114.2 ± 43.5*	88.5 ± 32.3††††
Plasma renin activity (ng/mL · hr)	3.1 ± 2.3	9.9 ± 5.2****	17.5 ± 11.4††††
Plasma aldosterone (ng/dL)	32.0 ± 30.7	130.5 ± 69.4***	202.5 ± 130.0††††
Plasma norepinephrine (pg/mL)	221.6 ± 68.2	571.1 ± 241.1****	965.0 ± 502.5††††
WHVP (mmHg)	28.0 ± 4.0	30.5 ± 4.0*	29.5 ± 5.0
FHVP (mmHg)	11.5 ± 3.0	11.0 ± 4.0	8.5 ± 3.5††
HVPG (mmHg)	16.5 ± 3.0	19.5 ± 3.0***	21.0 ± 4.0††
HBF (mL/min)‡	1,123 ± 328.0	948 ± 221.1	713 ± 188.4††††

NOTE. Data are presented as mean ± SD.

Abbreviations: MELD, Model for End-Stage Liver Disease; MAP, mean arterial pressure; HR, heart rate; RAP, right atrial pressure; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedged pressure; CO, cardiac output; SVR, systemic vascular resistance; WHVP, wedged hepatic venous pressure; FHVP, free hepatic venous pressure; HVPG, hepatic venous pressure gradient; HBF, hepatic blood flow.

*$P < .05$; **$P < .01$; ***$P < .005$; ****$P < .001$ with respect to baseline values of group A.

†$P < .05$; ††$P < .01$; †††$P < .005$; ††††$P < .001$ with respect to baseline values of group B.

‡A hepatic extraction greater than 10% was required for the calculation of hepatic blood flow in 15 patients of group A and 19 patients of group B.

In a multivariate analysis, the authors found only two variables independently associated with the development of HRS: Plasma renin activity (RR: 31.3; 95% CI 1.3-25.2; p< 0.05) and cardiac output (RR: 5.8; 95% CI: 6.5-150.3; p< 0.05). This study demonstrates that significant cardiac dysfunction exists at baseline in patients who go on to develop HRS. This so-called "cirrhotic cardiomyopathy" is a distinct entity from alcoholic heart muscle disease[11]. The mechanisms that lead to its development are not entirely clear. In the absence of known cardiac disease, mechanisms such as blunted contractile responsiveness to stress and/or altered diastolic relaxation are thought to play a role. Evidence of diastolic dysfunction in patients with advanced cirrhosis or HRS can be seen on echocardiography and at autopsy[12]. Moreover, systolic dysfunction may be unmasked by certain stresses, such as surgery or placement of a transjugular intrahepatic portosystemic shunt (TIPS). These events, especially TIPS, result in return of a significant amount of preload to a dysfunctional heart. This systolic dysfunction has been shown to normalize with time after TIPS placement[17]. Researchers are investigating the possibilities of altered cardiac beta-adrenergic receptor density and activity, as well as the negative inotropic effects of nitric oxide and bile acids[18]. Proposals for diagnostic criteria for cirrhotic cardiomyopathy are also being debated and defined[12]. At this time, however, the role of cirrhotic cardiomyopathy in the development of HRS has yet to be defined.

Treatment

Recent clinical advances have expanded treatment options for HRS. While liver transplant remains the treatment of choice, there are several pharmacologic and interventional options that are also available. Several pharmacologic options, such as the use of vasodilators and dopamine, have been abandoned due to poor patient outcomes in clinical trials, and lack of evidence regarding their efficacy[3]. Current clinical research is concentrating on the use of vasoconstrictors with or without the use of intravenous albumin. While their mechanism is incompletely understood, vasoconstrictors are believed to inhibit and reverse splanchnic vasodilatation, thus removing the stimulus for the activation of endogenous vasoactive systems, and reversing renal vasoconstriction4. The mechanism of action of albumin, and the clinical evidence supporting its use in HRS, remains elusive. The use of albumin in treatment of HRS is not universal. However, many authors and clinicians feel that albumin leads to more effective volume expansion than isotonic saline, thus increasing effective arterial volume[4].

While these alternative therapies have shown promise clinically, the number of clinical trials investigating their use remains scarce. The evidence for their efficacy is limited by the lack of randomized controlled trials and the small study populations used. Moreover, protocols for the use of these medications vary widely between studies, resulting in different doses of drugs and different titration parameters. Many of these clinical trials do not report data on survivability or factors that predict response to therapy. As a result, it is not yet known which patients will benefit from one modality versus another, or how these treatments impact the poor prognosis of HRS. At this stage, pharmacologic and interventional therapies can and should be seen as a bridge to transplantation, extending the window of opportunity for appropriate candidates to undergo a more definitive form of treatment of HRS.

Terlipressin

The use of vasopressin analogues had been proposed to improved renal blood flow over thirty years ago[19]. More recently, ornipressin was studied in patients with type 1 HRS, but was abandoned due to the high incidence of ischemic side effects[20]. Terlipressin is a vasopressin analogue that has been used in Europe for over 20 years for the treatment of variceal bleeding. To date, it is the most studied drug for the treatment of HRS[21-27]. It is an inhibitor of the V-1 receptor subtype, found in abundance on splanchnic vascular smooth muscle. While ornipressin must be given as a continuous intravenous infusion, terlipressin has the advantage of IV bolus dosing. Its use is limited in that it is not yet available in the United States. The most adverse effects of terlipressin administration are ischemic and arrhythmogenic events, but these have been relatively low (< 5%) in pooled studies of a total of 150 patients[3]. A positive or complete response to terlipressin (defined as a reversal of renal dysfunction to a serum creatinine level < 1.5mg/dL) has been shown in up to 60% of patients in the same pool of studies[3]. Despite being the most widely-studied drug for HRS, there are less than two dozen studies involving its use, and very few of these are randomized controlled trials.

Table 6. Design of clinical trials

Authors	Terlipressin dose, mg/day	Terlipressin duration (days)	Concomitant plasma-expander therapy
Hadengue *et al.*[17]	2.0	2.0	No
Duhamel *et al.*[18]	1.0–2.0	6.3+	No
Mulkay *et al.*[19]	2.0	26.0 (8–68)	12 (100%)
Alessandria *et al.*[20]	6.0	7	7 (100%)
Colle *et al.*[23]	2.0–4.0	9.1 ± 1.3	13 (72.2%)
Halimi *et al.*[21]	4.0 (1.5–12)	7.0 (2–16)	No
Ortega *et al.*[22] (2)	5.0 ± 0.6	8.5 ± 1	13 (100%)
Ortega *et al.*[22] (2)	4.7 ± 0.5	7.4 ± 1	No
Solanki *et al.*[24]	2.0	15.0	11 (91.7%)
Danalioglu *et al.*[25]	2–4	6 (3–14)	7 (100%)
Saner *et al.*[26]	6.0	6.0	7 (100%)

One such recent trial of 24 patients showed a significant improvement in renal function by day 8 in the treatment group as compared to controls (1.6 $\pm$ 0.01 vs. 3.9 $\pm$ 0.26, $p < 0.05$)[21]. However, survival at 15 days was limited to 5/12 patients in the treatment group, compared to 0/12 controls. This study used a fixed dose of terlipressin, whereas many studies used dose titrations based on hemodynamic parameters or response of renal function. Another confounder was the use of intravenous albumin and fresh frozen plasma, used to keep central venous pressure above 10-12cm of H_2O. A more recent, larger, randomized controlled trial showed significant improvements in renal function in the terlipressin group, but narrowly failed to achieve statistical significance in the primary end-point of the study (patient alive on day 15 with a serum creatinine $\leq$ 1.5mg/dL)[22].

In 2006, a meta-analysis of 10 clinical trials (154 patients) with terlipressin was conducted to investigate the rate of response to therapy[24]. This was defined as a decrease in serum creatinine to < 1.5mg/dL after therapy. Two of the 10 trials were randomized controlled trials. The authors also studied the rate of recurrence of HRS after treatment withdrawal, as reported in 6/10 trials included in the meta-analysis. Their results showed a pooled rate of response to therapy of 0.52 (95% CI 0.42-0.61, $p < 0.0001$). The pooled rate of recurrence after terlipressin withdrawal was 0.55 (95% CI 0.40-0.69; p = 0.00001). The drop-out rate, a measure of tolerability, was 0%. Survival data were not reported. As stated before, this meta-analysis was composed of studies with great variability in both design and clinical end-points measured. More studies are needed to assess morbidity and mortality with therapy, define the optimal treatment dose and schedule, and assess factors predicting response to therapy. One small, retrospective trial showed a 100% three-year survival rate of 9 patients treated for HRS with terlipressin before transplantation[23]. This is substantially greater than the previously reported 60% three-year survival rate post-transplant for patients with untreated HRS pre-transplant. These results show promise for terlipressin therapy in terms of improving outcomes after more definitive treatment, but larger, multi-center, randomized controlled trials are still needed. While overall studies have shown a significant improvement in renal function following treatment with terlipressin[6], but more research is needed to better define its role in treatment of HRS.

Midodrine and Octreotide

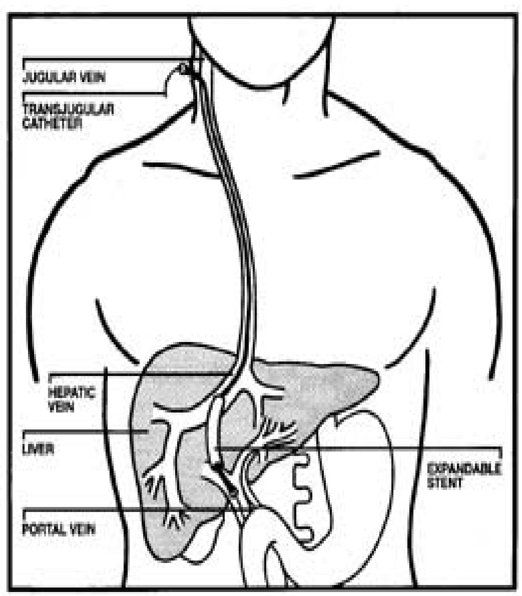
Several other vasoconstrictors have been studied for treatment of HRS, including the combination of midodrine and octreotide. Each medication has been used separately in clinical trials, but neither drug alone shows effectiveness in treating HRS[28, 29]. This is not surprising, especially for midodrine, given the resistance of the splanchnic circulation to vasoconstrictors. There is emerging evidence of success in treatment of HRS with the combination of midodrine and octreotide[30-32]. Midodrine is an orally available alpha-adrenergic agonist, and functions as a vasoconstrictor. Octreotide, given subcutaneously, is a somatostatin analogue. This is the major inhibitory hormone of the gastrointestinal tract, and antagonizes the actions of various splanchnic vasodilators such as NO and glucagon[33]. Adverse effects of midodrine include headaches, urinary retention, and hypertensive episodes. Octreotide can interfere with glucose metabolism, leading to hypoglycemia. One advantage can readily be seen with this combination compared to terlipressin: route of administration. The oral and subcutaneous routes, respectively, may permit outpatient use of this combination for treatment of HRS in selected settings, if long-term efficacy and survival can be demonstrated.

As with all the therapies for HRS, the data regarding this combination's efficacy is sparse. One recent, retrospective, single-center study evaluated the efficacy of therapy and mortality rates with midodrine and octreotide[32]. 60 patients with a diagnosis of type 1 HRS who were treated with midodrine/octreotide were compared to 21 untreated controls. There were no significant differences between groups at baseline. It is interesting to note that intravenous albumin was not used as part of the treatment protocol. However, it was used as the fluid of resuscitation to make the diagnosis of HRS, as per the IAC criteria, in both case and control patients. The authors also list specific dosing schedules for octreotide and midodrine, as well as dose adjustment parameters for the latter. As in other trials, a response to therapy was measured as a reduction in serum creatinine to < 1.5mg/dL during the inpatient hospitalization. The authors found a significant response to therapy (24/60 case patients vs. 2/21 controls, p = 0.01) at 30 days. They also showed significantly improved 30-day survival in treated vs. untreated patients (26/60 vs. 15/21 deaths, p = 0.03). A high rate of loss to follow up (attributed to the poor socioeconomic status of this center's patient population) precluded the extension of this data to three and six month rates, as per the initial study design. Also, the study showed a statistically significant effect of midodrine dosing on reduction of serum creatinine at 30 days, with a higher rate of response to therapy at higher doses ($p = 0.03$). This same effect was not observed with the higher dose of octreotide. Medication dosing had no statistically significant effect on 30-day survival. Of the treated patients who were alive at 30 days, two went on to have TIPS performed, while one received a liver transplant. Despite its retrospective design, this study is valuable in that it reports not only rate of response, but also survival data as well. Randomized controlled trials with more longitudinal follow-up are needed in the future, but results are promising for this combination therapy.

Wong, et al. reported on the use of combination midodrine/octreotide, followed by TIPS when applicable, in a pilot study of 14 patients with type 1 HRS[30]. Medical therapy for an average of 14 $\pm$ 3 days improved serum creatinine in 10 of the 14 patients. Five of these ten went on to receive TIPS placement, with a continued improvement in serum creatinine at 12 months (96 $\pm$ 20 µmol/min vs. 233 $\pm$ 29 :mol/min pre-TIPS, p <0.01). This demonstrates the possibility of medical therapy as a bridge to more definitive treatment for HRS.

Transjugular Intrahepatic Portosystemic Shunting (TIPS)

The development of progressive cirrhosis with portal hypertension is a prerequisite to the development of the circulatory dysfunction seen in HRS. It stands to reason, therefore, that correcting the underlying portal hypertension may stop the cascade of events towards HRS before it even starts. With this in mind, TIPS has been studied as a potential therapy for HRS. Studies have shown a 30-50% mortality rate at one year after ascites has become diuretic resistant[34]. The role of TIPS in managing refractory ascites has been studied previously, showing proven efficacy in this context[34].



From a physiologic standpoint, TIPS is thought to decompress the portal circulation, thereby lowering portal pressures and thus returning splanchnic volume to the systemic circulation. This in turn increases EAV, downregulates the activity the RAAS, and prohibits renal vasoconstriction. Results of recent trials have shown significant improvements in both renal function and survival in patients with HRS[35,36]. However, many patients were excluded from these trials based on the severity of their liver disease[34]. Elevations in serum bilirubin and prothrombin time, as well as a history of severe encephalopathy or a Child-Pugh score greater than 11 preclude many patients from receiving a TIPS. Unfortunately, many patients with HRS, especially type 1 HRS, present with such clinical manifestations. Since refractory ascites is the clinical end-result of type 2 HRS, there may be a role for TIPS in the management of this subset of patients, but it has yet to be fully elucidated.

Liver Transplantation

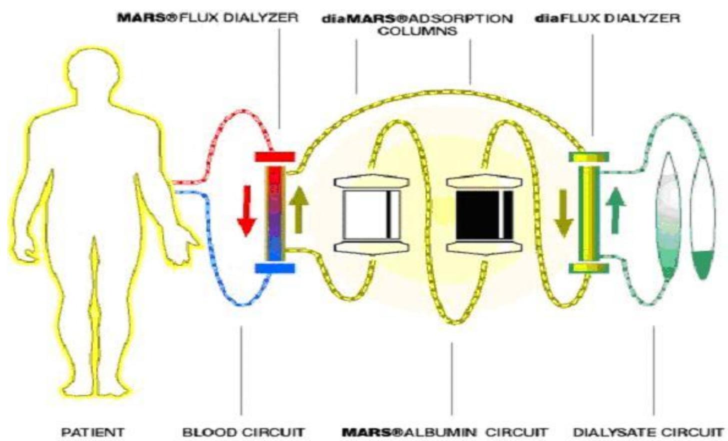
Liver transplantation remains the best treatment option for suitable candidates with HRS3. This modality offers a cure to both the underlying liver disease and the circulatory and renal dysfunction that can result. This option is limited by a number of factors, chiefly the availability of organs for transplant and the short survival of patients with type 1 HRS. Most patients with HRS, especially type 1 HRS, die while waiting for an organ to become available for transplant[4]. Priority for transplant in the United States is assigned by the MELD (Model for End-Stage-Liver-Disease) scoring system, which calculates a score based on three patient variables: serum creatinine, bilirubin, and international normalized ratio (INR)[3]. Priority is given to those with a higher MELD score. There are, however, instances where patients with HRS may have near normal bilirubin and INR levels despite an elevated serum creatinine. This may not give these patients a high enough MELD score to move them up the waiting list. Other countries have different allocation systems, and give a higher priority to patients with HRS[3].

It is well established that pre-transplant renal dysfunction predicts a poorer outcome following liver transplant[37-40]. Patients with HRS also have more complications following transplant, including more ICU days, a higher post-operative mortality rate, and a higher percentage of patients who require dialysis in the post-operative period (35% vs. 5% without HRS)[37]. Despite these complications, survival rates following transplantation are quite good for patients with HRS. The United Network of Organ Sharing (UNOS) reports a 50% five-year survival rate for patients with a pre-transplant serum creatinine level > 2.0mg/dL regardless of the cause[40]. Data from various studies reports an overall survival rate of 60% at 3 years for patients with HRS, as compared to 70-80% in patients without HRS[37-39]. Data also indicate a significant improvement in renal function as early as 90 days post-transplant in HRS patients[37]. This trend has been shown to continue over time. This contrasts to an overall decline in renal function observed in non-HRS patients. The decline is thought to be secondary to the nephrotoxic effects of the immunosuppressive regimen used in the post-transplant period. Overall, however, HRS patients have decreased renal function compared to their non-HRS counterparts post-transplant.

The role of treatment of HRS becomes more critical, given the above data. Preliminary studies of treatment pre-transplant on post-transplant outcomes show promising results. Restuccia et al. showed a 100% three-year survival rate post-transplant in 9 patients treated with terlipressin and albumin pre-transplant[23]. These results need to be duplicated with prospective, randomized controlled trials to confirm treatment benefits on transplant outcomes. Successful treatment of HRS could prolong survival time, and increase the chances of patients receiving a transplant.

Extra-Corporeal Albumin Dialysis

Conventional methods of dialysis have not been well-studied, but results from uncontrolled trials show that they are ineffective in reversing or improving HRS[3]. Renal replacement therapy has been routinely used to manage the complications of progressive renal dysfunction in these patients, particularly continuous modes given the presence of hypotension[40]. Recently, an extracorporeal albumin dialysis system was developed in Germany. This involves the use of an albumin-containing dialysate circuit, which is connected to a conventional dialysis apparatus[4]. This allows for the removal of albumin-bound substances and toxins, including ammonia, bile acids, medium-chain fatty acids, and copper[4]. The Molecular Adsorbent Recirculating System (MARS) has been investigated for use in acute-on-chronic liver failure, fulminant liver failure, and more recently for HRS[41-44]. While it has received 501(k) approval for use in the United States for treating overdoses and poisonings[45], experience with this system is quite limited. Results from early trials in HRS do show decreases in serum creatinine[42], but it is unclear if this is simply an effect of the filtration system. Moreover, hemodynamics have not been monitored in studies with HRS, and preliminary survival data are limited[3]. Due to the lack of conclusive data, this therapy is still viewed as largely experimental. With more encouraging data, this may become a new therapeutic tool in treatment of HRS, serving as a possible bridge to transplantation.



Conclusion

Hepatorenal syndrome is an extreme complication of cirrhosis and end-stage liver disease. The challenges in its diagnosis are equaled by the limited options for its effective treatment. The pathophysiology of the syndrome lies at the center of future investigations. Improved understanding of the mechanisms of this syndrome will bring more effective treatment options. Much work remains in studying the available modalities, and assessing their efficacy in treating hepatorenal syndrome. These therapeutics may be able to extend the bridge to liver transplantation, giving more patients hope for a cure.

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