Treatment of hepatorenal syndrome

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Hepatorenal syndrome is an uncommon but potentially fatal complication of decompensated cirrhosis. The major pathogenetic factor is systemic arterial vasodilatation with effective arterial underfilling and renal vasoconstriction. Treatment options are aimed at correcting the arterial vasodilatation and effective arterial underfilling, thereby improving renal perfusion. Possible treatment options include vasoconstrictor therapy, transjugular intrahepatic portosystemic stent shunt, and extracorporeal dialysis. Definitive treatment for hepatorenal syndrome is liver transplantation, and patients should preferably have their renal dysfunction corrected prior to liver transplant in order to improve post-transplant outcome. [*Indian J Gastroenterology* 2006;25(Suppl 1):S8-S12]

The development of hepatorenal syndrome (HRS) in a patient with advanced liver cirrhosis carries a grave prognosis, with mean survival of 7-10 days if left untreated.[1] Until a few years ago, there were no effective treatments except for liver transplantation. Over the past decade, with better understanding of the pathophysiology that occurs in advanced cirrhosis and the pathogenesis of HRS, several treatment options are now evolving. An updated definition of HRS also helps to better define the patients for treatment for HRS.

In November 2005, the International Ascites Club held a Focused Group Meeting at the American Association for Study of Liver Diseases meet to standardize the nomenclature and diagnostic criteria for HRS in light of recent findings on pathophysiology of HRS. Three important new concepts have arisen to explain the pathogenesis of HRS:[1] the most important pathophysiological change that leads to the development of HRS is a profound disturbance of the systemic hemodynamics with severe arterial vasodilatation, which is partly sustained by a relative inefficient cardiac output;[2] systemic arterial vasodilatation occurring mainly in the splanchnic circulation, whereas in other vascular beds such as the renal and cerebral circulations, there is vasoconstriction, which can lead to organ dysfunction;[3] type 1 HRS is frequently caused by a precipitating event; one of the most frequent triggers is bacterial infection, with spontaneous bacterial peritonitis (SBP) being the most frequent precipitating

Hepatorenal Syndrome
Pathophysiology - Summary

First Hit

Second hit

Second hit

Sinusoidal portal Hypertension

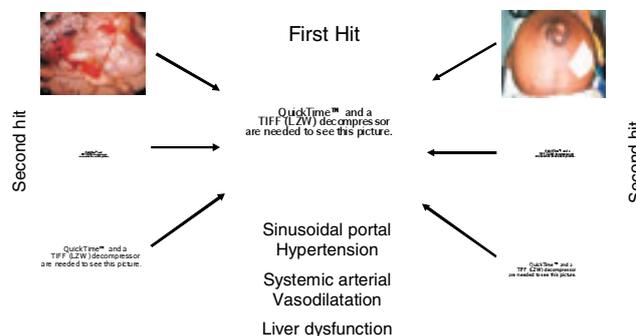Systemic arterial Vasodilatation

Liver dysfunction

Fig 1: Pathophysiology of hepatorenal syndrome

event (Fig 1).

Definition and diagnostic criteria

With the improved knowledge of the pathogenesis, HRS is now defined as a potentially reversible syndrome that occurs in patients with cirrhosis, ascites and liver failure. It is characterized by impaired renal function and marked abnormalities in cardiovascular function and activity of endogenous vasoactive systems. In the kidney, there is marked renal vasoconstriction that results in low glomerular filtration rate. In the extra-renal circulation there is arterial vasodilatation that is located in the splanchnic circulation. A similar syndrome may also occur in acute liver failure.

Table 1 lists the updated diagnostic criteria for HRS. The important changes from the previous diagnostic criteria of 10 years ago[2] include the

Table 1: Diagnostic criteria for hepatorenal syndrome

• Cirrhosis with ascites
• Serum creatinine over 1.5 mg/dL (133 μmol/L)
• No improvement of serum creatinine (decrease of serum creatinine equal to or less than 1.5 mg/dL [133 μmol/L]) after at least 48 h of diuretic withdrawal and volume expansion with albumin. The recommended dose of albumin is 1 g/Kg b.w 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, micro-hematuria (>50 RBC/high power field) and/or abnormal renal ultrasound

International Ascites Club, November 2005

Table 2: Types of hepatorenal syndrome

Type 1

- Rapid reduction in renal function in <2 weeks, defined as

  Doubling of initial serum creatinine to >2.5 mg/dL

  or 50% reduction of the initial 24-hour creatinine

clearance to <20 mL/min

- Occurs in patients who are severely ill with jaundice and coagulopathy
- Most often precipitated by bacterial infection, particularly SBP
- Frequently associated with multi-organ failure

Type 2

- Renal function slowly deteriorates over weeks to months
- Occurs in cirrhotic patients with refractory ascites
- Patients are usually less ill with only mild jaundice and coagulopathy

recognition that cardiac dysfunction specific to cirrhosis, or cirrhotic cardiomyopathy, plays a role in the pathogenesis of the relative ineffective cardiac output that contributes to the hemodynamic instability in these patients. Furthermore, it is now recognized that colloids rather than crystalloids are the preferred volume expanders to refill the expanded intravascular volume.

Hepatorenal syndrome clinically is divided into 2 types (Table 2). Type 1 HRS has a rapid onset, occurs in the very sick patients with advanced liver failure, and is frequently precipitated by some event. If left untreated, type 1 HRS is associated with a prognosis of days to weeks. Type 2 HRS, in contrast, occurs in patients with cirrhosis and refractory ascites. The patient is usually less ill and the renal function just slowly deteriorates over weeks to months.

Treatment

Each treatment option aims at correcting some aspects of the pathophysiology that leads to the development of HRS.

Vasoconstrictor therapy

The aim of using vasoconstrictor therapy is to increase systemic or splanchnic vasoconstriction. The former improves renal perfusion pressure, while the latter redistributes part of the splanchnic volume to the systemic circulation, thereby improving the systemic arterial blood volume, with consequent improved renal perfusion and glomerular filtration. The vasoconstrictor that is approved for treatment for HRS in Europe is terlipressin, a vasopressin analogue. To date, there are approximately 180 patients

treated in the published literature. The infusion of terlipressin at a dose of 0.5-2 mg/4-6 h intravenously up to 15 days was associated with improved renal function, suppressed plasma renin activity and aldosterone levels, and increased atrial natriuretic factor levels, with some improvement of urinary sodium excretion, all without serious side effects, in approximately two-thirds of the patients.[3,4,5]

Terlipressin is not approved for the treatment of HRS in North America. Therefore, the alternative combination of midodrine and octreotide has been used to treat HRS. Midodrine is an oral α-adrenergic agonist that improves systemic blood pressure and hence improves renal perfusion pressure. Octreotide is a long-acting analogue of somatostatin, which antagonizes the action of various splanchnic vasodilators and reduces the mismatch between the extent of arterial vasodilatation and the intravascular volume. This combination has been studied in a total of 19 patients.[6,7] Once again, there was a significant improvement in both the systemic and renal hemodynamics and urinary sodium excretion in approximately two-thirds of patients, although the renal function did not return to normal, despite suppression of all measured neurohormonal systems to within their normal ranges. It should be noted that octreotide alone has not been shown to be effective as a treatment for HRS.[8] The doses of the drugs and the routes of administration were very different in the two studies that used midodrine and octreotide. In general, the dose of midodrine should be titrated to give a mean arterial pressure of >95 mmHg. An intravenous infusion of octreotide would be preferred over the subcutaneous route since this gives a constant dose of a drug that has a very short half-life.

Albumin has been used in combination with vasoconstrictor therapy in the treatment of HRS. The rationale for using albumin is several-fold. Albumin is a negatively charged molecule; it therefore attracts sodium, which in turn retains water. Therefore, it is useful as a volume expander. Albumin also has ligand binding and anti-oxidant properties,[9] and therefore potentially is useful in clearing the various toxins that have vasodilatory properties. Thus, albumin can improve intravascular filling and potentially could also reduce the extent of systemic arterial vasodilatation. While some authors believe that the use of albumin can improve the efficacy of vasoconstrictor therapy,[10] the largest retrospective study on the use of terlipressin for HRS did not find any difference in the outcome of patients irrespective of whether albumin was added to terlipressin or not.[4]

Table 3: Published studies on use of TIPS as treatment for HRS

Author	n	year	Type of study	Creatinine pre-TIPS	Creatinine post-TIPS	Survival
Lake	8	1993	R	3.2 (0.9) mg/dL	Decreased by 1.4 mg/dL (5) unchanged (3)	4/8 3 with Tx
Spahr	1	1995	case report	6mg/dL	normal	2 months
Brensing	16	1997	PU (I &II)	226 (140) µm/L	104 (52) µm/L	9/16
Guevara	7	1998	PU (I)	5.0 (0.8) mg/dL	1.8 (0.4) mg/dL	140 (68) days
Brensing	41	2000	PU (I & II)	2.3 (1.7) mg/dL	1.5 (1.2) mg/dL	75 (14) weeks
Testino	18	2003	PU (II)	1.9 (0.5) mg/dL	0.9 (0.3) mg/dL	12/18 Tx
Wong	5	2004	PU (I)	25 (4) mL/min (GFR)	96 (20) mL/min (GFR)	17 (5) months

R: retrospective study, PU: Prospective uncontrolled study, I= Type 1 HRS, II= Type II HRS

Currently, there are no guidelines as to whether albumin should be used or not in conjunction with vasoconstrictor therapy in the treatment of HRS, nor are there guidelines on the dose of albumin to be administered should the physician decide to use it. Given the fact that albumin has volume-expanding, ligand-binding and anti-oxidant properties, it seems prudent to use albumin in the treatment of HRS unless there is evidence that it actually does some harm.

Transjugular intrahepatic portosystemic stent shunt (TIPS)

Sinusoidal portal hypertension plays a pivotal role in the control of renal hemodynamics[11] by modulating renal sympathetic nervous activity.[12] TIPS functions as a side-to-side portocaval shunt and is very effective in lowering portal pressure. It is therefore not surprising that the insertion of TIPS, especially in cirrhotic patients with refractory ascites and some degree of renal dysfunction, is associated with improvement in both glomerular filtration rate and renal blood flow.[7] In addition, TIPS returns a significant portion of the splanchnic volume into the systemic circulation, leading to suppression of various vasoactive neurohormones, resulting in better renal perfusion.

There are only a few studies evaluating the clinical effect of TIPS in patients with type 1 or type 2 HRS.[7,13-18] Most have focused on subjects with type 1 HRS, while one study each investigated type 2 HRS alone[16] or a mixed population of types 1 and 2 HRS.[13,14] Unfortunately, there are no controlled studies comparing TIPS to other modalities of treatment, in particular vasoconstrictors plus albumin. The great majority of the studies were retrospective and either did not have a control group or did not have pre-defined methods for assigning subjects to TIPS versus control therapy.

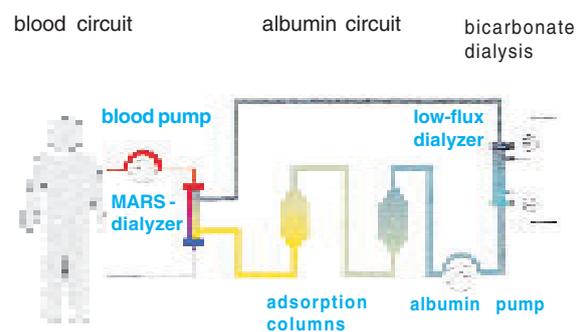Table 3 lists all the published studies on the use of TIPS as a treatment for HRS. We can conclude that TIPS produced improvement in renal function in all reported studies, but it does not normalize renal function. Despite this, TIPS appears to confer a survival advantage over conventional medical therapy in subjects with HRS.[7,14] It is interesting to note that when TIPS was placed after a period of vasoconstrictor therapy,[7] renal function returned to near normal levels. In that particular study, some of the patients who normalized their renal function post-TIPS have survived for more than 2 years without liver transplantation, once again emphasizing the functional nature of this condition.

Extracorporeal albumin dialysis (ECAD)

ECAD is a system that uses a cell-free, albumin-containing dialysate that is re-circulated and perfused through charcoal and anion exchange columns. This procedure enables the removal of albumin-bound substances. One such system is known as molecular adsorbent recirculating system (MARS) (Fig 2). The potential benefits of ECAD in patients with cirrhosis and renal dysfunction are the removal of cytokines released by precipitating factors such as infection, superimposed hepatitis, or gastrointestinal bleeding.

Treatment of Hepatorenal Syndrome

Albumin Dialysis

blood circuit   albumin circuit   bicarbonate dialysis

blood pump   low-flux dialyzer

MARS - dialyzer

adsorption columns   albumin pump

Fig 2: Molecular adsorbent recirculating system (MARS), one of the extracorporal albumin dialysis systems

To date, there are 15 patients in the published literature who have received ECAD as a treatment for type 1 HRS. Eight patients were included in a randomized trial comparing MARS with "standard therapy",[19] while the other seven patients with HRS received MARS as a treatment for acute-on-chronic liver failure due to alcoholic hepatitis.[20] There was significant improvement in serum creatinine and bilirubin levels, associated with improved systemic hemodynamics. Since the ECAD removes creatinine and bilirubin as part of the dialysis system, reduction in serum creatinine does not necessarily mean an improvement in renal function, as none of the studies assessed glomerular filtration rate. However, ECAD must have removed sufficient "toxins" that are vasodilators to lead to an improvement in systemic hemodynamics. Furthermore, the use of MARS seems to confer some survival advantage over standard treatments, although survival with MARS treatment is still dismal without liver transplantation.[19]

Currently, there is insufficient data to support the routine use of ECAD as a treatment for HRS, especially since ECAD is an expensive and labor-intensive procedure, each session lasting 6-8 hours. However, the treatment does hold some promise. Firm recommendation for the use of ECAD will have to await the results of well-designed randomized controlled trials comparing ECAD versus vasoconstrictor therapy, which is now regarded as the standard therapy for HRS.

Liver transplantation

Liver transplantation remains the only effective permanent treatment for hepatorenal syndrome, as it corrects liver dysfunction and eliminates portal hypertension. Furthermore, during the actual procedure of liver transplantation, there is a major effort to optimize systemic hemodynamics and blood pressure, thus increasing renal perfusion. Thus, liver transplantation improves renal function, together with reduction in plasma levels of vasoactive factors.[21] Patients who are transplanted with HRS have a lower probability of both graft and patient survival after liver transplantation, compared to patients without hepatorenal syndrome. Furthermore, patients with HRS require longer stay in intensive care units, longer hospitalization, and more dialysis treatments after liver transplantation.[22] In fact, the pre-transplant serum creatinine[23] and the duration of pre-transplant renal dysfunction predict post-transplant outcome,[24] with those patients with the higher pre-transplant serum creatinine and the longer duration of pre-transplant renal dysfunction more likely to maintain their high serum creatinine at 12 months post transplant. In fact, the duration of the pre-transplant renal dysfunction has been advocated as a criterion for selecting patients for combined liver-kidney transplantation. In those patients whose HRS is treated prior to liver transplantation, the post-transplantation clinical outcome is significantly improved, being similar to patients transplanted without HRS.[25] Therefore, in patients with end-stage cirrhosis awaiting liver transplantation, every attempt should be made to improve renal function in order to maximize the post-transplantation outcome.[26]

Current practice and guidelines

Currently, there are no standard guidelines for the treatment of HRS in the transplant setting. It also appears that the diagnostic criteria used to diagnosis HRS is not uniform. Patients with cirrhosis and renal dysfunction are frequently started on standard dialysis and maintained on it until liver transplantation. Thus, there is also an urgent need to standardize the diagnosis of HRS. The recommended first-line treatment should be pharmacotherapy and, depending on the local availability of drugs, it could be either terlipressin or midodrine and octreotide and albumin. The doses used should be titrated to give a mean arterial blood pressure of >95 mmHg. The albumin dose should be 1 g/Kg body weight with a maximum dose of 100 g per day. The duration of treatment has not been agreed on, but the combination should continue until the renal function has plateaued for at least 3 to 4 days.

TIPS can be used as a second line of treatment, either to follow pharmacotherapy or without preceding pharmacotherapy, but patient suitability for TIPS insertion may limit its application. Table 4 lists the recommended patient selection criteria for TIPS insertion. Currently there is not sufficient data to recommend the use of ECAD as a treatment for HRS. Randomized controlled trials comparing ECAD versus vasoconstrictor therapy are needed but this will take a lot of efforts as ECAD is expensive and labor-intensive.

Table 4: Patient selection criteria for TIPS insertion

Definite contraindications	Relative contraindications
Pre-existing hepatic encephalopathy (>Grade I)	Any infection including dental sepsis
Cardiopulmonary diseases	Non-compliance with Na
Pulmonary hypertension	restriction in patients
Hepatoma	with ascites
Portal vein thrombosis	
Child Pugh score =12	

Liver transplantation is the recommended treatment of choice for HRS, and patients should be referred earlier rather than later, as the pre-transplant renal function does have an impact on the post-transplant outcome.

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