Review article: hepatorenal syndrome – how to assess response to treatment and nonpharmacological therapy

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SUMMARY

Hepatorenal syndrome (HRS) is a complex syndrome. In addition to severe reduction of renal function due to renal vasoconstriction, there is impairment in systemic haemodynamics, activation of the renin-angiotensin and sympathetic nervous systems and antidiuretic hormone, vasoconstriction of the brain, muscle and skin, and dilutional hyponatraemia. Treatment in patients with type 2 HRS, the most frequent form of HRS, is directed towards managing refractory ascites. Paracentesis is the treatment of choice. TIPS is also effective but is more expensive, is associated with higher incidence of hepatic encephalopathy, and does not increase survival. Although a rapidly progressive renal failure is the most characteristic manifestation of type 1 HRS, there is failure in other organs such as the liver and the brain. A decrease in cardiac output develops in these patients, associated with a decrease in cardiopulmonary pressures. Since type 1 HRS mainly occurs in patients with spontaneous bacterial peritonitis and massive release of cytokines within the peritoneal cavity, it may be considered as a special form of multiorgan failure of circulatory origin. Not surprisingly, the treatment of choice in type 1 HRS is the combination of vasoconstrictors to reduce arterial vasodilation and plasma volume expansion with albumin to increase cardiac preload. TIPS is also effective in these patients and the combination of pharmacological treatment followed by TIPS may be the most effective approach.

CLINICAL CHARACTERISTICS AND PATHOGENESIS

Hepatorenal syndrome (HRS) is a functional renal failure that develops in patients with cirrhosis as a consequence of an extreme renal vasoconstriction.[1–10] The International Ascites Club has defined HRS as a decrease in creatinine clearance below 40 mL/min or an increase in serum creatinine over 1.5 mg/dL in the absence of data suggesting other types of renal failure (nephrotoxicity, prerenal azotemia due to volume depletion, glomerulonephritis, obstructive uropathy) (Table 1).[2] There are two types of HRS: Type 2 HRS,

the most frequent form, is a steady renal failure of moderate intensity (serum creatinine between 1.5 and 2.5 mg/dL). The main clinical problem associated with this type of HRS is a lack of response to diuretic therapy and refractory ascites. In contrast, type 1 HRS is an acute, progressive and severe renal failure. It frequently develops in patients who already have type 2 HRS in

Table 1. Major diagnostic criteria of HRS (International Ascites Club)

1.	Hepatic failure and portal hypertension
2.	Creatinine >1.5 mg/dL or GFR <40 mL/min
3.	No shock, no ongoing bacterial infection, nephrotoxic agents or fluid losses
4.	No improvement after diuretic withdrawal and intravenous saline infusion (1500 mL)
5.	Proteinuria < 500 mg/day, normal renal echography

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close chronological association with an event that acts as a precipitating factor. The most frequent complication associated with type 1 HRS is a severe bacterial infection, particularly spontaneous bacterial peritonitis (SBP). Patients with type 1 HRS die within 1–3 weeks after the onset of renal failure in terminal hepatic and renal failure (jaundice, hepatic encephalopathy, severe renal failure, oliguria or anuria).

HRS occurs in the setting of severe impairment in circulatory function characterized by arterial hypotension and marked homoeostatic activation of the renin-angiotensin system, sympathetic nervous system and antidiuretic hormone.[11–13] In addition to vasoconstriction in the renal circulation, there is increased resistance in other arterial vascular compartments such as the muscle, skin and brain. Vasoconstriction in these territories is a compensatory mechanism to maintain arterial pressure. For many years circulatory dysfunction in HRS was considered to be due to an accentuation of the splanchnic arterial vasodilation already present in patients with nonazotemic cirrhosis with ascites. In type 2 HRS the accentuation of the arterial vasodilation would be slowly progressive and secondary to the natural course of the disease. In type 1 HRS, however, it would be acute, severe and promoted by the precipitating event. Studies in patients with SBP support this concept. Type 1 HRS develops in patients with an intense inflammatory response (very high plasma and ascitic fluid levels of cytokines) and in the setting of an acute decrease in arterial pressure and an intense stimulation of the renin-angiotensin and sympathetic nervous systems and antidiuretic hormone.

Recent studies assessing systemic haemodynamics prior to and after the development of HRS, however, clearly indicate that the pathogenesis of circulatory dysfunction associated with HRS is far more complex.[14] The development of HRS occurs in the absence of significant changes in peripheral vascular resistance, which is compatible with an aggravation of the decrease in peripheral vascular resistance compensated by the increased activity of the renin-angiotensin and sympathetic nervous systems. However, there is also a significant decrease in cardiac output indicating a contribution of the heart in the pathogenesis of this abnormality. HRS occurs in the setting of a simultaneous decrease in peripheral vascular resistance and an impairment of cardiac function. Since cardiopulmonary pressures also decrease (L. Ruiz del Arbol, unpubl. observations), a most likely mechanism of the impairment in cardiac output is a central hypovolaemia related to a decrease in venous return.

HOW TO ASSESS TREATMENT OF HRS

Although the aim of this article is to review the nonpharmacological treatment of HRS, some mention must be made of the treatment of HRS with plasma volume expansion and vasoconstrictors, since most data concerning assessment of response in these patients derives from studies using this therapy; albumin and vasoconstrictors are the initial treatment of choice in patients with type 1 HRS.

At present there are several studies[15–21] showing that: (1) type 1 HRS is reversible following treatment with intravenous albumin and vasoconstrictors (Table 2). Normalization of serum creatinine occurs after 7–14 days of treatment in 60–75% of patients. Treatment for shorter periods of time improves circulatory function (suppression of plasma renin activity and noradrenaline (norepinephrine) concentration but not renal function. The aim of the treatment should be to reduce serum creatinine below 1.5 mg/dL. Recurrence of HRS after stopping treatment is rare in this circumstance but frequent if renal function is only partially improved; (2) the two components of the treatment are important since HRS does not reverse when vasoconstrictors or plasma volume expansion are given alone. This feature is consistent with the concept that HRS is secondary to the simultaneous occurrence of central hypovolaemia and increase in splanchnic arterial vasodilation; (3) the constant infusion of vasoconstrictors (ornipressin or noradrenaline [norepinephrine]) is associated with ischaemic complications, a feature not

Table 2. Effect of vasoconstrictors (ornipressin and terlipressin) and volume expansion in HRS (from Guevara M et al.[15] and Uriz J et al.[17])

	Baseline (n = 15)	Day 3 (n = 12)	Day 7 (n = 9)	Day 14 (n = 7)
MAP (mmhg)	70 ± 8	70 ± 8	77 ± 9	79 ± 12
PRA (ng/mL/h)	1 ± 15	4 ± 2	2 ± 3	1 ± 1
NE (pg/mL)	1257 ± 938	550 ± 382	550 ± 410	316 ± 161
Creatinine (mg/dL)	3 ± 1	3 ± 1	2 ± 1	1 ± 1

Results are given as mean ± SD.
Normal values: PRA < 1.4 ng/mL/h; NE < 260 pg/mL; $P < 0.001$ for all values (ANOVA).
MAP = mean aortic pressure; PRA = plasma renin activity; NE = noradrenaline.

observed when vasoconstrictors (terlipressin [Glypressin®] – or midodrine) are given intermittently; (5) there is a delay of several days between the improvement in circulatory function, as estimated by a marked suppression of plasma renin activity and noradrenaline (norepinephrine) concentration, and the increase in glomerular filtration rate (GFR); (6) reversal of HRS improves survival and a significant number of patients may reach liver transplantation. Long-term administration of albumin and vasoconstrictors is therefore the initial treatment of choice in type 1 HRS; (7) although serum creatinine normalizes in most patients and creatinine clearance increases, there is no normalization in GFR. Creatinine clearance remains between 30 and 50 mL/min in most patients.

Although some studies have demonstrated that volume expansion with albumin and vasoconstrictors also reverses renal failure in patients with severe type 2 HRS, the experience in these patients is still limited.[16] In patients with moderate type 2 HRS the main clinical problem is refractory ascites. According to the International Ascites Club the treatment of choice in these patients is total paracentesis plus albumin infusion. Transjugular intrahepatic portosystemic shunt (TIPS) may be indicated only in those patients requiring very frequent paracentesis.[22] TIPS markedly reduces the need for paracentesis. However patients require diuretic treatment to prevent the reappearance of ascites and the incidence of hepatic encephalopathy is high.

Response to pharmacological treatment in patients with type 1 HRS is assessed by sequentially measuring serum creatinine concentration during therapy. Measurement of arterial pressure, plasma renin activity and serum sodium concentration is also useful. A significant increase (around 10 mmHg) of arterial pressure indicates an appropriate dosage of the vasoconstrictor agent. Plasma renin activity rapidly decreases when there is a positive response. Nevertheless, serum creatinine is the most important parameter for the assessment of therapeutic response. If there is no significant reduction in serum creatinine within the first 2 days of treatment, the dosage of the vasoconstrictor should be increased irrespective of the change in arterial pressure. As indicated previously, treatment should be continued until serum creatinine decreases to less than 1.5 mg/dL otherwise the possibility of HRS recurrence after stopping therapy is high. Cases without significant decrease in serum creatinine within the first 4–5 days of treatment will not respond and other therapies (i.e.

TIPS) are indicated. It is interesting to note that despite the use of analogues of vasopressin (terlipressin), improvement in serum creatinine is consistently associated with an increase in serum sodium concentration and disappearance of the dilutional hyponatraemia present in these patients. This indicates that impairment in free water clearance in cirrhosis is more related to renal failure than to high plasma levels of antidiuretic hormone.

NONPHARMACOLOGICAL TREATMENT OF HEPATORENAL SYNDROME

Liver transplantation

Liver transplantation is the treatment of choice for HRS[23–28] but its clinical applicability is low, particularly in patients with type 1 HRS. Survival of cirrhotic patients with type 2 HRS is sufficiently prolonged to enable them to receive a liver graft. However this is not the case in patients with type 1 HRS, in whom the expected survival is less than 2 weeks. Reversal of HRS by pharmacological treatment improves survival in a significant number of patients, and they may be able to be transplanted. TIPS (see below) may also serve as a bridge until liver transplantation. Living donor liver transplantation can be indicated in these patients.

Immediately after transplantation a further impairment in GFR may be observed and many patients require haemodialysis (35% of patients with HRS compared to 5% of patients without HRS). Because ciclosporin or tacrolimus may contribute to this impairment in renal function, it has been suggested that administration of these drugs should be delayed until a recovery of renal function is noted, usually 48–72 h after transplantation. After this initial impairment in renal function, GFR starts to improve and reaches an average of 30–40 mL/min by 1–2 months postoperatively. This moderate renal failure persists during follow-up, is more marked than that observed in transplantation patients without HRS, and is probably due to a greater nephrotoxicity of ciclosporin or tacrolimus in patients with renal impairment prior to transplantation. The haemodynamic and neurohormonal abnormalities associated with HRS disappear within the first month of operation and patients regain a normal ability to excrete sodium and free water.[29]

Patients with HRS who undergo transplantation have more complications, spend more days in the intensive care unit, and have a higher in-hospital mortality rate

than transplantation patients without HRS.[23–28] However there is good long-term survival of patients with HRS who undergo liver transplantation, with a 3-year probability of survival of 60%.[23–28] This survival rate is only slightly reduced compared to that of transplantation in patients without HRS (which ranges between 70% and 80%). There is a pilot study showing that morbidity and survival of patients with HRS treated with albumin infusion and vasoconstrictors before liver transplantation have a post-transplantation outcome similar to that of patients transplanted with normal renal function,[30] suggesting that treatment of HRS improves the results of liver transplantation.

Transjugular intrahepatic portosystemic shunt (TIPS)

Since portal hypertension is the initial event of the circulatory dysfunction in cirrhosis, the decrease of portal pressure by portacaval anastomosis is a rational approach for the treatment of HRS. There are several case reports showing reversal of HRS following surgical portosystemic shunt.[31, 32] However, the applicability of major surgical procedures in patients with HRS is small. The development of TIPS has reintroduced the idea of treating HRS by reducing portal pressure.

Four studies assessing TIPS in the management of type 1 HRS have been reported[33–36] and were recently reviewed by Brensing et al.[37] In total, 30 patients were treated. In two series no liver transplantation was performed, whereas in the other two series three out of nine patients were transplanted 7, 13 and 35 days after TIPS. TIPS insertion was technically successful in all patients. Only one patient died as a consequence of the procedure. GFR improved markedly within 1–4 weeks after TIPS and stabilized thereafter. In one study specifically investigating the neurohormonal systems, improvement in GFR and serum creatinine was related to a marked suppression of the plasma levels of renin and antidiuretic hormone.[34] The suppression of plasma noradrenaline (norepinephrine) is lower than that of renin, a feature also observed in refractory ascites treated by TIPS. Follow-up data concerning hepatic function was obtained from 21 patients. De novo hepatic encephalopathy or deterioration of pre-existing hepatic encephalopathy occurred in nine patients, but in five it could be controlled with lactulose. Survival rates based on the 27 patients without early liver transplantation at 1, 3 and 6 months were 81%, 59% and 44%, respectively. These studies strongly suggest that TIPS is

useful in the management of type 1 HRS. Studies comparing TIPS with pharmacological treatment in type 1 HRS are needed.

Peritoneo-venous shunting

For many years peritoneo-venous (LeVeen) shunt was considered an effective therapy for refractory ascites and HRS. However, this procedure is rarely used today. There is a randomized trial demonstrating that peritoneo-venous shunting is ineffective in type 1 HRS,[38] and in type 2 HRS with refractory ascites it does not improve the results obtained with therapeutic paracentesis.[39, 40] LeVeen shunts are associated with severe complications such as superior vena cava thrombosis or intestinal obstruction and a high rate of shunt obstruction requiring re-operation, so that this therapy has been abandoned.

Other therapeutic methods

Haemodialysis and arterio-venous or veno-venous haemofiltration are frequently used in patients with HRS, but their efficacy has not been adequately assessed.[41] Recently, extracorporeal albumin dialysis, a system that uses an albumin-containing dialysate that is recirculated and perfused trough a charcoal and anion-exchanger column, has been shown to improve systemic haemodynamics and reduce the plasma levels of renin in patients with type 1 HRS.[42, 43] In a small series of patients an improved survival has been reported. Further studies are needed to confirm these findings.

PREVENTION OF HRS

Two randomized controlled studies in large series of patients have shown that HRS can be prevented in specific clinical settings. In the first study,[44] the administration of albumin (1.5 g/kg intravenously at diagnosis of infection and 1 g/kg intravenously 48 h later) together with cefotaxime in patients with cirrhosis and SBP markedly reduced the incidence of impairment in circulatory function and the occurrence of type 1 HRS compared to a control group of patients receiving cefotaxime alone (10% incidence of HRS in patients receiving albumin vs. 33% in the control group). Moreover, the hospital mortality rate (10% vs. 29%) and the 3-month mortality rate (22% vs. 41%) were lower in patients receiving albumin. In a second

study,[45] the administration of the tumour necrosis factor inhibitor pentoxyfilline (400 mg t.i.d) to patients with severe acute alcoholic hepatitis reduced the occurrence of HRS (8% in the pentoxyfilline group vs. 35% in the placebo group) and hospital mortality (24% vs. 46%, respectively). Since bacterial infections and acute alcoholic hepatitis are two important precipitating factors of type 1 HRS, these prophylactic measures may decrease the incidence of this complication.

CONCLUSION

HRS is a major clinical turning point in patients with cirrhosis. Although the most characteristic feature of the syndrome is a renal failure due to renal vasoconstriction, it is a more generalized process affecting the heart, brain and the splanchnic organs. There are two types of HRS. Type 1 HRS is characterized by a rapidly progressive impairment in circulatory and renal function. It usually develops in close relationship with a precipitating event, particularly severe bacterial infections, and is associated with a poor prognosis (median survival less than 2 weeks). Type 2 HRS is characterized by a steady impairment in circulatory and renal function. Patients with type 2 HRS have a median survival of 6 months and their main clinical problem is refractory ascites. The pathogenesis of HRS is a deterioration in effective arterial blood volume due to splanchnic arterial vasodilatation and reduction in venous return and cardiac output. Long-term administration of intravenous albumin and vasoconstrictors or the correction of portal hypertension with TIPS are effective treatments of HRS, improve the survival, and may serve as a bridge to liver transplantation, which is the treatment of choice in these patients.

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