

Hepato-Renal Syndrome in Patients with Hepatic Cirrhosis

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ABSTRACT Hepatorenal syndrome is a particular form of functional renal failure which may develop in patients with liver cirrhosis. Precise diagnostic criteria have been established to clearly define this entity, whereas recent advances in the understanding of the biology of vasoactive mediators and the physiology of microcirculation have allowed to better anticipate its pathophysiological mechanisms. During the course of cirrhosis, sinusoidal portal hypertension leads to splanchnic and systemic vasodilation, responsible for a reduction of effective arterial blood volume. As a result, a state of intense renal vasoconstriction develops, leading to renal failure in the absence of any organic renal disease. Innovative therapies have shown promise to prolong survival in patients with hepatorenal syndrome, including the administration of analogs of vasopressin, the insertion of transjugular intrahepatic portosystemic shunts. On a preventive viewpoint, several simple measures have been shown to reduce the risk of hepatorenal syndrome in cirrhotic patients including the appropriate use of diuretics, the avoidance of nephrotoxic drugs, the prophylaxis of spontaneous bacterial peritonitis and optimal fluid management in patients undergoing large volume paracentesis.

KEY WORDS *hepatorenal syndrome, cirrhosis, renal failure, pathophysiology, treatment, prevention*

Introduction

Hepatorenal syndrome (HRS) is a functional renal failure occurring most often in the context of the evolution of a severe hepatic cirrhosis (Child C) with portal hypertension and ascites. There are rare cases associated with severe acute liver failure. SHR is expressed by a oligoanurie and azotemia as a result of a decline in renal blood flow and glomerular filtration. The kidney initially purely functional is associated with hyperinflation and water and a high cardiac output, illustrating the importance of local traffic, especially mesenteric and renal disturbances. The challenge of resuscitation is to restore adequate renal perfusion without increasing the patient and water overload or damage the local traffic through the use of inappropriate catecholamines. HRS is a research area where the rich innovations, particularly in the therapeutic area are numerous.

Renal failure and liver cirrhosis

Cirrhotic patients are especially vulnerable to kidney failure, either by the occurrence of complications. The most important complication is Hepatorenal Syndrome. This represent a specific entity within the context of liver cirrhosis and it is the result of humoral and hemodynamic disorders encountered in an advanced stage of the disease.

In more than 90% of cases, renal failure occurring in the cirrhotic is the result of renal hypoperfusion(5).

HRS is classified into two subtypes, 1 and 2, depending on severity and mode of presentation of renal failure. HRS type 1 occurs in the terminal stage of severe cirrhosis Child C, with a rapidly progressive evolution toward irreversible renal failure. It is defined by the doubling of creatinine in two weeks to more than 130 mol / l. The previously normal renal function or altered slightly, the acute renal failure, and the absence of organic cause, or other obvious question promotes guide to the diagnosis of type 1 HRS(3).

HRS type 2 corresponds to the slow and gradual formation of a mild renal insufficiency during cirrhosis, responding favorably to a diuretic chronic and repeated paracentesis. However, the move towards a type 1 HRS is common during precipitating events such as spontaneous bacterial peritonitis, acute alcoholic hepatitis, or gastrointestinal bleeding related to portal hypertension(6).

Creatinine is an insensitive test to detect the drop in glomerular filtration in patients cirrhotic often malnourished and whose protein catabolism is low. The uremia is more sensitive, although the hepatic chronic liver reduces its synthesis.

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-hr creatinine clearance <40 ml/min

-Absence of shock, bacterial infection, and current or recent treatment with nephrotoxic drugs; absence of gastrointestinal fluid losses (repeated vomiting or diarrhea) or renal fluid losses (weight loss >500 g/day for several days in patients with ascites without peripheral edema or 1000 g/day 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/day and no ultrasonographic evidence of obstructive uropathy or parenchymal renal disease

Additional criteria

-Urine volume <500 ml/day

-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

(International Ascites Club's Diagnostic Criteria of Hepatorenal Syndrome**Arroyo V, Gine's P, Gerbes A, et al (3).

Pathogenesis of SHR

SHR results from a collapse of renal perfusion related to the combined effects of intense vasoconstriction of the renal arteries and a diminution of renal blood flow following arterial vasodilation territories splanchniques and systemic(1). Vasodilation splanchnique, induced by excessive secretion of vasodilatory substances such as NO is the initial event responsible for a phenomenon of filling in on the territories then arterial hypotension. In a second time, it occurs an activation of systems vasoconstrictive (renin-angiotensin, adrenaline and noradrenaline, vasopressin, endothelin) with the aim of restoring the hemodynamic status. These systems vasoconstrictors cause a decrease in renal perfusion and flow filtration glomerular without alteration of tubular function, unlike what is observed in acute tubular necrosis. The activation of vasoconstrictor systems is also involved in salt retention (renin-angiotensin, adrenaline and noradrenaline) and free water (antidiuretic hormone).

Although the mechanisms are not completely understood, it is accepted that portal hypertension takes a major role in the development of hemodynamic abnormalities described above. The

beneficial effect of TIPS in patients with HRS or conversely, the early decrease in renal blood flow observed after occlusion of the TIPS with a ball are the recent demonstrations of the direct contribution of portal hypertension in the pathogenesis of HRS(8). The severity of hepatocellular insufficiency is also involved in the pathogenesis of HRS.

HRS occurs in patients with severe hepatocellular insufficiency and those with little to moderate impairment of liver function.

The pathophysiologic hallmark of HRS is severe vasoconstriction of the renal circulation(9). 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 HRS1.

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). Experimental evidence has shown that mild increases in portal pressures lead to the upregulation of nitric oxide synthase. Along with overproduction, these vasodilators escape hepatic degradation due to portosystemic collateralization and advanced liver dysfunction inherent in cirrhotics. 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, including the renin-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(10). 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(3). The resulting arterial hypotension from splanchnic vasodilatation causes a decrease in systemic vascular resistance. This decrease 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(11). Some investigators postulate that cardiac dysfunction is present in patients with HRS, and may contribute to its underlying pathophysiology.

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Clinical aspects

The first step in the diagnosis of HRS is the demonstration of a reduced GFR. The muscle mass and the release of creatinine is reduced in these patients and they may present normal or only moderately increased serum creatinine concentration in the setting of a very low GFR.

There is consensus to establish the diagnosis of HRS when serum creatinine has risen above 1.5 mg/dl.

The second step is the differentiation of HRS from other types of renal failure.

For many years this was based on the traditional parameters used to differentiate functional renal failure from acute tubular necrosis (urine volume, urine sodium concentration). Acute tubular necrosis in patients with cirrhosis and ascites usually courses with oliguria, low urine sodium concentration, and urine osmolality greater than plasma osmolality. Relatively high urinary sodium concentration has been observed in patients with HRS and high serum bilirubin.

Because of the lack of specific tests, diagnosis of HRS is based on the exclusion of other disorders that can cause renal failure in cirrhosis(5).

Acute renal failure of pre-renal origin due to renal (diuretics) or extrarenal fluid losses should be investigated. If renal failure is secondary to volume depletion, renal function improves rapidly after volume expansion, whereas no improvement

occurs in HRS. Even if there is no history of fluid losses, renal function should be assessed after diuretic withdrawal and volume expansion to rule out any subtle reduction in plasma volume as the cause of renal failure. The presence of shock before the onset of renal failure points toward the diagnosis of acute tubular necrosis. Cirrhotic patients with infections may develop transient renal failure, which resolves after resolution of the infection. This occurs in approximately one third of patients(12,13). HRS in cirrhotic patients with bacterial infections should be diagnosed in patients without septic shock and only if renal failure does not improve following antibiotic administration. Cirrhotic patients are predisposed to develop renal failure in the setting of treatments with aminoglycosides, nonsteroidal anti-inflammatory drugs and vasodilators (renin-angiotensin system inhibitors, nitrates)(14). Treatment with these drugs in the days preceding the diagnosis of renal failure should be ruled out. Finally, patients with cirrhosis can develop renal failure due to intrinsic renal diseases, particularly glomerulonephritis in patients with hepatitis B or C (deposition of immunocomplexes) or with alcoholic cirrhosis (deposition of IgA). These cases can be recognized by the presence of proteinuria, hematuria or both, or abnormal renal ultrasonography (small irregular kidneys with abnormal echostructure).

Treatment of HRS

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. Treatment is aimed at improving renal perfusion, primarily by reversing vasodilation. Long-term administration (1-2 weeks) of vasoconstrictors is associated with improved renal function.

The treatment goal for these agents is a reduction in serum creatinine to <1 mg/dl. The use of these agents may induce ischemic events, such as myocardial infarction, that require frequent monitoring(electrocardiogram, cardiac enzyme). Other treatment considerations include discontinuing diuretics, nephrotoxic agents, and vasodilatory agents such as beta-blocking agents. Fluid resuscitation with albumin or isotonic saline may be cautiously attempted. Albumin should be administered to patients with SBP as it reduces the rate of renal dysfunction, including HRS. Renal support therapy may be used to bridge patients until liver function improves or liver

transplantation occurs. Transjugular intrahepatic portosystemic shunt insertion temporarily improves renal function. The only therapy proven to normalize and sustain renal function is liver transplantation.

Treatments for type-1 HRS

Liver Transplantation

Liver transplantation is the treatment of choice for any patient with advanced cirrhosis, including those with type-1 and type-2 HRS. Immediately after transplantation, a further impairment in GFR may be observed and many patients require hemodialysis.

After this initial impairment in renal function, GFR starts to improve and reaches an average of 30 to 40 mL/min by 1 to 2 months postoperatively. This moderate renal failure persists during follow-up and is more marked than that observed in transplantation patients without HRS and is probably due to a greater nephrotoxicity of cyclosporine or tacrolimus in patients with renal impairment prior to transplantation. The hemodynamic and neurohormonal abnormalities associated with HRS disappear within the first month after the operation and patients regain a normal ability to excrete sodium and free water. The long-term survival of patients with HRS who undergo liver transplantation is good, with a 3-year probability of survival of 60%. The main problem of liver transplantation in type-1 HRS is its applicability. Treatment of HRS with vasoconstrictors and albumin increases survival in a significant proportion of patients decreases early morbidity and mortality after transplantation, and prolongs long-term survival.

Vasoconstrictors and Albumin

Treatment of HRS with vasoconstrictors and albumin increases survival in a significant proportion of patients decreases early morbidity and mortality after transplantation, and prolongs long-term survival. The iv administration of vasoconstrictor agents (vasopressin, ornipressin, terlipressin, noradrenaline) or iv or subcutaneous octreotide during 1 to 3 weeks is an effective treatment of type-1 HRS. An important observation was that type-1 HRS does not recur after discontinuation of the treatment in most patients. A retrospective survey in 99 patients with type-1 HRS admitted to 22 hospitals in France and treated with terlipressin and albumin (70% of cases) showed a rate of improvement in renal function of 58%. The probability of survival was 40% at 1 month and 22% at 3 months. Improvement of survival was related to reversal of HRS.

These studies clearly indicate that vasoconstrictors associated with iv albumin should be recommended for the management of patients with type-1 HRS since they normalize serum creatinine in a high proportion of patients and may improve survival(15). Terlipressin has been the most widely used vasoconstrictor agent in type-1 HRS. It is very effective and is associated with a low incidence of side effects. Terlipressin dosage should be progressive, starting with 0.5 to 1 mg/4 to 6 h. If serum creatinine does not decrease by more than 30% in 3 days, the dose should be doubled. The maximal dose of terlipressin has not been defined, although there was consensus that patients not responding to 12 mg/day will not respond to higher doses. Albumin should be given starting with a priming dose of 1 g/kg of body weight followed by 20 to 40 g/day. It is advisable to monitor central venous pressure. In patients responding to therapy, treatment should be continued until normalization of serum creatinine (<1.5 mg/dl).

Transjugular Intrahepatic Portosystemic Shunt (TIPS)

TIPS is effective in normalizing serum creatinine in a significant proportion of patients with cirrhosis and severe azotemia and is an alternative treatment to vasoconstrictors in type-1 HRS.

Extracorporeal Albumin Dialysis

The decrease in serum creatinine observed in most patients could be related to the dialysis process. Clear beneficial effects were observed on systemic hemodynamics and on hepatic encephalopathy.

Treatments for type-2 HRS

In patients with type-2 HRS, most of whom may reach a liver transplant, the main clinical problem is refractory ascites. Therefore, treatment of type-2 HRS should

consider not only survival but also the control of ascites.

Transjugular Intrahepatic Portosystemic Shunt

Five trials comparing TIPS versus paracentesis in patients with refractory or recidivant ascites have been published. Data from these five trials are not valid for the assessment of TIPS in the management of patients with type-2 HRS. The introduction of covered stents should be a stimulus to re-evaluate the role of TIPS in the management of refractory ascites and type-2 HRS.

Vasoconstrictors and Albumin

The current state of knowledge on vasoconstrictor therapy in type-2 HRS is therefore

very poor. It appears to be not as effective as in type-1 HRS due to the high rate of HRS recurrence.

Prevention of HRS

The administration of albumin (1.5 g/kg iv at infection diagnosis and 1 g/kg iv 48 hours later) to patients with cirrhosis and SBP markedly reduced the incidence of circulatory dysfunction and type 1 HRS (10% incidence of type-1 HRS in patients receiving albumin versus 33% in the control group). Hospital mortality rate (10% versus 29%) and the 3-month mortality rate (22% versus 41%) were lower in patients receiving albumin.

Oral norfloxacin may prevent type-1 HRS. Several studies have shown that in patients with cirrhosis in addition to bacterial translocation there is translocation

of products of bacterial origin (endotoxin, bacterial DNA) that induce a systemic inflammatory reaction, activation of nitric oxide, and impairment in circulatory function. The administration of oral norfloxacin in these patients prevents this translocation of bacterial products and improves circulatory function with a significant

increase in arterial pressure and systemic vascular resistance and suppression of plasma renin activity and plasma norepinephrine concentration.

Bacterial infections and acute alcoholic hepatitis are important precipitating factors of type 1 HRS and the prophylactic measures may decrease the incidence of this complication.

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