Cheung *et al. Hepatoma Res* 2017;3:67-72
DOI: 10.20517/2394-5079.2016.48

Hepatoma Research
www.hrjournal.net

Minireview Open Access

Updates on hepatorenal syndrome and strategies bridging to liver transplantation

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How to cite this article: Cheung CY, Chok KSH. Updates on hepatorenal syndrome and strategies bridging to liver transplantation. Hepatoma Res 2017;3:67-72.

Article history:
Received: 01-12-2016
Accepted: 08-02-2017
Published: 12-04-2017

Key words:
Hepatorenal syndrome,
liver cirrhosis,
terlipressin,
liver transplantation,
portal hypertension,
acute kidney injury

ABSTRACT

Hepatorenal syndrome is not an uncommon life-threatening complication arising from liver cirrhosis. The diagnostic criteria for this syndrome have been revised throughout the years, with recent revisions aimed at improving earlier diagnosis and treatment. Liver transplantation remains the only definitive treatment for hepatorenal syndrome. Due to the scarcity of liver grafts, many patients die waiting. This review focuses on the different strategies to bridge patients to liver transplantation and to improve the postoperative outcome.

DEFINITION OF HEPATORENAL SYNDROME

Hepatorenal syndrome (HRS) is the deterioration of renal function resulting from cirrhosis.[1] Portal hypertension leads to splanchnic vasodilatation, accompanied by gradual decrease in systemic vascular resistance.[2] The fall in systemic arterial pressure, or so-called "arterial under filling", is compensated by an increase in cardiac output by activating the renin-angiotensin-aldosterone system and sympathetic nervous system, which causes vasoconstriction of renal arteries.[3] Resulting renal hypoperfusion, together with sodium and water retention and hypoalbuminemia due to poor synthetic function of the liver, causes decreased glomerular filtration rate (GFR), ascites, and edema.[1,4]

Diagnostic criteria of HRS have been revised throughout the years. They were initially defined by the International Ascites Club (IAC) in 1996, based on major and minor criteria to characterize the occurrence of renal failure in cirrhotic patients.[5] Major criteria can be summarized as the presence of liver failure and portal hypertension and acute renal failure, while excluding shock, ongoing sepsis, nephrotoxic drug, hypovolemia, nephrotic syndrome,

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and obstructive uropathy.[6] Urinary output, sodium, osmolality and red blood cells, and serum sodium were included as minor criteria [Table 1]. These criteria were subsequently revised in 2007 to improve accuracy and applicability.[7] Minor criteria were excluded. Ongoing bacterial infection without septic shock was no longer an exclusion criterion [Table 1].

Two types of HRS have been described. Type-1 HRS is characterized by acute onset and rapidly progressing kidney failure with a doubling of serum creatinine (corresponding to a 50% reduction of creatinine clearance) in less than 2 weeks. The prognosis is poor, with only 10% of patients surviving longer than 90 days. Type-2 HRS presents as a less severe and more gradual decline in renal function associated with refractory ascites. The differential diagnosis between the two types is based on the rate of progression and extent of renal impairment.[3,8] In this review, we mainly focus on type-1 HRS as it is more clinically relevant in terms of strategies bridging to liver transplantation. Treatment of type-2 HRS with terlipressin and albumin does not appear to have beneficial effects either in pretransplantation or in posttransplantation outcomes.[9]

According to the IAC criteria, acute renal failure is defined as an increase in serum creatinine (sCr) of ≥ 50% from baseline to a final value > 1.5 mg/dL (133 mol/L). However, the threshold value of 1.5 mg/dL has been challenged. Meanwhile, new definition of acute renal failure, now termed acute kidney injury (AKI), has been developed and validated in patients without cirrhosis. Combining the emerging evidence and consensus of the experts, the IAC revised the criteria of AKI in patients with cirrhosis (type-1 HRS) in 2015.[10] In the new definition, AKI is defined as a sCr increase of ≥ 0.3 mg/dL (26.5 umol/L) within 48 h or of ≥ 50% from baseline within 7 days [Table 1]. Three stages of AKI and responses to treatment were also defined. The implementation of the new criteria is to allow earlier treatment of patients with type-1 HRS, which may lead to a better outcome instead of having to wait until the sCr reaches ≥ 2.5 mg/dL.[11]

STRATEGIES TO BRIDGE TO LIVER TRANSPLANTATION

Medical treatment aims to stabilize the patients until liver transplantation and to optimize their pre-transplant clinical conditions.[4] Treatment strategies target the underlying pathophysiological mechanism of HRS, including exerting splanchnic vasoconstriction and renal vasodilatation in combination with volume expansion.[12,13] Many studies have suggested that the use of vasopressor plus volume expansion with intravenous albumin improves prognosis of HRS. A significant proportion of patients was successfully bridged to liver transplantation.[9,13-16] Human serum albumin has been introduced as a plasma expander since 1940 and it has been proved useful in the management of HRS.[17] The additive effects provided by vasoconstrictors and albumin infusion improve outcome compared to monotherapy with either agent.[18] A meta-analysis has demonstrated that increments of 100 g in cumulative albumin dose were associated with a significantly increased survival, which provides evidence on the important role of albumin in improving outcome of treating HRS.[19]

The most commonly used vasopressor is terlipressin. Terlipressin is a prohormone of lysine-vasopressin (three glycyl residues and lysine-vasopressin). The glycyl residues are cleaved from the prohormone by endothelial peptidases, allowing prolonged release of lysine-vasopressin.[20,21] This mechanism enables divided-dose administration by prolonging the half-life of terlipressin, in contrast to the need for continuous infusion as with vasopressin. Terlipressin acts on the V1 receptors expressed on vascular smooth muscle cells in the splanchnic circulation.[22] The vasoconstrictive effect corrects the circulatory dysfunction and intrarenal vasoconstriction, which lowers the levels of renin and serum creatinine and improves the urine output. As a result of breaking the vicious cycle, the kidney regains its normal self-regulatory function. Gluud *et al*.[15] performed a meta-analysis in 2012 involving 6 randomized controlled trials of terlipressin (with or without albumin) *vs*. placebo, with a total of 309 patients. Use of terlipressin was associated with reduced mortality with a relative risk of 0.76 (95% CI 0.61-0.95). Concurrent use of terlipressin and albumin increased the number of patients with reversal of HRS.

Side-effects of terlipressin include abdominal cramps and diarrhea, cardiac tachyarrhythmia and chest pain, as well as cyanosis and livedo reticularis. Ischemia of bowel or skin and extremities is one of the rare complications.[23] The adverse effects of terlipressin may be minimized by means of intravenous infusion rather than bolus injections as shown in a recent randomized controlled study in Italy.[24] Although most commonly used and studied, terlipressin is expensive and unavailable in many countries. Other vasoconstrictive agents are used as well. An association between increase in arterial pressure and therapeutic response has been found.[25]

Noradrenaline, a catecholamine with predominantly alpha-adrenergic activity, is widely available and inexpensive and has been used for the treatment of

Table 1: Comparison of three versions of the International Ascites Club diagnostic criteria of HRS-1

1996	2007	2015
Major criteria	**Criteria**	**Criteria**
Chronic or acute liver disease with advanced hepatic failure and portal hypertension	Presence of cirrhosis with ascites	Presence of cirrhosis with ascites
Low glomerular filtration rate: sCr > 1.5 mg/mL or 24 h sCr clearance < 40 mL/min	sCr > 1.5 mg/dL	Diagnosis of acute kidney injury (increase in sCr ≥ 0.3 mg/dL or 1.5 times over baseline)
No sustained improvement in renal function following diuretic withdrawal and expansion of plasma volume with at least 1,500 mL of isotonic saline	No improvement of sCr after at least 2 days of diuretic withdrawal and volume expansion with albumin (1 g/kg of body weight per day up to a maximum of 100 g/day)	No improvement of sCr after at least 2 days of diuretics withdrawal and volume expansion with albumin (1 g/kg of body weight per day up to a maximum of 100 g/day)
Absence of shock, ongoing bacterial infection	Absence of shock	Absence of shock
No treatment with nephrotoxic drugs or gastrointestinal or renal fluid losses	No current or recent treatment with nephrotoxic drugs	No current or recent treatment with nephrotoxic drugs
Proteinuria < 0.5 g/day and no evidence of obstructive nephropathy or parenchymal renal disease on ultrasound	No macroscopic signs of structural kidney injury: normal findings on renal ultrasonography, absence of proteinuria > 500 mg/day and absence of microhematuria	No macroscopic signs of structural kidney injury: normal findings on renal ultrasonography, absence of proteinuria > 500 mg/day and absence of microhematuria
Additional criteria		
Urinary volume < 0.5 L/day		
Urinary sodium < 10 mmol/L		
Urinary osmolality > plasma osmolality		
Urinary red blood cells < 50/HPF		
Serum sodium < 130 mmol/L		

HRS: hepatorenal syndrome; sCr: serum creatinine; HPF: high power field

HRS since 2002.[26] A meta-analysis in 2014 identified four small randomized trials comparing noradrenaline and terlipressin in the treatment of HRS.[27] The 4 studies comprising 154 patients showed no differences between terlipressin and noradrenaline in reversal of HRS, mortality at 30 days, and recurrence of HRS. Adverse events, mainly abdominal cramps, were less common with noradrenaline.

Midodrine is another alpha-adrenergic agent commonly used in the United States as an alternative to terlipressin, and is used in combination with octreotide and albumin. Skagen *et al*.[28] reported a case control study comparing 75 HRS patients who received the triple therapy with a historical cohort of 87 HRS patients who did not. It showed a significantly better transplant-free survival, overall survival and renal function at 1 month.

Besides the use of vasopressors and albumin, transjugular intrahepatic portosystemic shunt (TIPS) and extracorporeal albumin dialysis were also used to treat HRS in some centers. TIPS is a percutaneously created low-resistance channel between portal vein and hepatic vein with the aim of reducing the portal pressure by shunting blood from the portal to the systemic circulation.[29] Few studies have evaluated the effectiveness of TIPS in treating HRS. In 6 out of 7 patients with type 1 HRS, renal function improved 30 days after TIPS, which was associated with a significant reduction in activity of the renin-angiotensin and sympathetic nervous systems.[30] Another small study also demonstrated an improvement in renal function after TIPS in 18 patients with type 2 HRS awaiting orthotopic liver transplant.[31] A non-randomized comparative study of 41 HRS patients (31 with TIPS performed, and another 10 in which TIPS was contraindicated due to advanced liver failure), type 1 and 2 included, showed that renal functions improved 2 weeks after TIPS and with better survivals.[32] However, the study was heavily biased towards the intervention arm due to patient selection. Wong *et al*.[33] further demonstrated in their case series the additional benefit of TIPS on top of Midodrine, octreotide and albumin, in improving renal function and sodium excretion for type 1 HRS patients. Despite these evidence, TIPS is a risky procedure, if not contraindicated, in HRS patients requiring liver transplantation who have advanced liver failure. Procedural-related mortality was also reported.[32] Thus, the role of TIPS in bridging HRS patients to liver transplantation remains limited to selected patients.

Renal replacement therapy (RRT) has been provided to cirrhotic patients with acute kidney injury, with indications no different from other patients with acute kidney injury. However, the renal failure was caused by HRS in only 13% of these patients.[34] The 3-month survival was only 15% in these patients without liver transplant, which was the lowest comparing to

parenchymal renal failure, hypovolemia or infection associated renal failure.

Molecular adsorbent recirculating system (MARS) was used in bridging fulminant hepatic failure and acute on chronic hepatic failure patients to orthotopic liver transplantation.[35] It represents a cell-free liver dialysis or albumin dialysis, and helps to remove albumin-bound substances accumulating in liver failure.[36] A randomized controlled trial by Mitzner *et al*.[37] compared type 1 HRS patients treated with volume expansion, dopamine, and haemodynamic filtration *vs*. the same plus MARS. The result showed a significantly better survival for treatment group at 1 month. Even though there was improvement of 1-month survival, one criticism of the study was that it only had one long-term survivor (more than 1 month) and thus it had little clinical relevance. The improvement in serum creatinine and bilirubin may merely reflect the effect of albumin dialysis, without a significant change in liver and renal function.[38] Further trials to evaluate this strategy will be needed.

LIVER TRANSPLANTATION

Liver transplantation is the definitive treatment of HRS. However, due to the scarcity of liver grafts, most patients died while awaiting transplantation.[2] Acute liver decompensation with type-1 HRS has worse outcome after liver transplantation than that without HRS. Chok *et al*.[39] reported 104 patients with acute liver decompensation who received living donor liver transplantation. Among them, 33 patients had HRS. These 33 patients had longer stay in the intensive care unit, more hemodialysis, more blood transfusions, worse postoperative renal function at 1 year and poorer overall survival. However, 5-year overall survival was still nearly 80%, which is satisfactory. The authors concluded that living donor liver transplantation should be considered for such patients. Other centers also reported similar outcome.[40,41] Some patients with a longer duration of type-1 HRS before liver transplantation were reported to have non-reversal of HRS after transplantation. Wong *et al*.[42] analyzed the 15 patients with non-reversal of HRS among the 62 HRS patients with liver transplantation. They found a 6% increased risk of non-reversal with each additional day of pre-transplant dialysis. This has illustrated that timely liver transplantation can improve the outcome of HRS patients.

PERIOPERATIVE USE OF TERLIPRESSIN AND REVERSAL OF HRS IN LIVER TRANSPLANTATION

There are little data regarding the role of perioperative use of terlipressin in liver transplantation. Patients with reversal of HRS before liver transplantation were reported to have a similar postoperative outcome to patients without HRS.[43] However, Rodriguez *et al*.[9] reported a contradicting result. In their cohort of 46 patients with type-2 HRS who underwent liver transplantation, 15 patients received terlipressin and albumin and had reversal of type-2 HRS. The remaining 31 patients had either relapse or no response or did not receive terlipressin and albumin. The 2 groups had no significant differences with respect to development of postoperative acute kidney injury, frequency of chronic kidney disease at 1 year, and 1-year and 3-year survival.

A randomized controlled trial was conducted to compare the hemodynamic effects of perioperative terlipressin infusion during living donor liver transplantation.[44] In this trial, intraoperative terlipressin infusion significantly decreased hepatic and renal arterial resistive indices, portal venous blood flow and systemic arterial pressure with lower systemic vascular resistance. The need for intraoperative vasoactive support was reduced. Terlipressin was continued for three postoperative days. Postoperative renal function was better in the terlipressin group.

FUTURE PERSPECTIVES

HRS is a life-threatening complication of liver cirrhosis and carries a poor prognosis. With a better understanding of the pathophysiology and advances in therapeutic strategies, there is hope to reduce its prevalence and improve patient outcome. Vasopressor treatment, such as that with terlipressin together with volume expander (i.e. albumin), has been shown to be an important strategy to stabilize patients and bridge them to liver transplantation, which is the only definitive treatment. It would be interesting to know the impact on prognosis in future after revising the diagnostic criteria and initiating treatment in an earlier phase. Moreover, studies showed contradicting results on whether the short-term survival benefit of terlipressin in patients with HRS, or the reversal of HRS, would translate into a better long-term outcome after liver transplantation. Further well-designed trials are needed to address this question.

Authors' contributions

Design of the review: K.S.H. Chok
Literature review and manuscript writing: C.Y. Cheung
Manuscript revision: K.S.H. Chok

Financial support andsponsorship

None.

Conflicts of interest

There are no conflicts of interest.

Patient consent

There is no patient involved.

Ethics approval

This review paper is waived for ethics approval.

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