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EDITORIAL

Current position of vasoconstrictor and albumin infusion for type 1 hepatorenal syndrome

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Abstract

Spontaneous bacterial peritonitis (SBP), refractory ascites, hepatorenal syndrome (HRS), hyponatremia and hepatic encephalopathy are complications which frequently happen during a clinical course of decompensated cirrhosis. Splanchnic and peripheral vasodilatation, increased intrarenal vasoconstriction and impaired cardiac responsive function are pathological changes causing systemic and hemodynamic derangement. Extreme renal vasoconstriction leads to severe reduction of renal blood flow and glomerular filtration rate, which finally evolves into the clinical feature of HRS. Clinical manifestations of type 1 and type 2 HRS come to medical attention differently. Patients with type 1 HRS present as acute kidney injury whereas those with type 2 HRS will have refractory ascites as the leading problem. Prompt diagnosis of type 1 HRS can halt the progression of HRS to acute tubular necrosis if the combined treatment of albumin infusion and vasoconstrictors is started timely. HRS reversal was seen in 34%-60% of patients, followed with decreasing mortality. Baseline serum levels of creatinine less than 5 mg/dL, bilirubin less than 10 mg/dL, and increased mean arterial pressure of over 5 mmHg by day 3 of the combined treatment of vasoconstrictor and albumin are the predictors of good response. Type 1 HRS can be prevented in some conditions such as albumin infusion in SBP, prophylactic antibiotics for upper gastrointestinal hemorrhage, albumin replacement after large volume paracentesis in cirrhotic patients with massive ascites. The benefit of albumin infusion in infection with primary source other than SBP requires more studies.

Key words: Albumin; Acute kidney injury; Hepatorenal syndrome; Cirrhosis; Vasoconstrictor

Core tip: Type 1 hepatorenal syndrome (HRS), which presents as acute kidney injury, is an uncommon, but critical problem in decompensated cirrhosis. The most common precipitating factor is infection especially spontaneous bacterial peritonitis. The combined regimen of albumin and vasoconstrictor is the pharmacotherapy

of choice for type 1 HRS based on pathogenic mechanisms of peripheral and splanchnic vasodilatation. Prompt treatment with the combined regimen can lead to HRS reversal in 34%-60% of patients. Type 1 HRS can be prevented in cirrhotic complications such as albumin infusion for spontaneous bacterial peritonitis, large volume paracentesis with albumin replacement, and prophylactic antibiotics for upper gastrointestinal hemorrhage.

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DEFINITION AND TYPES OF HEPATORENAL SYNDROME

In 2004, the Acute Dialysis Quality Initiative workgroup developed a consensus definition and classification for a new terminology of acute renal failure which was termed acute kidney injury (AKI) to reflect the entire spectrum of acute renal failure[1]. In 2007, the AKI Network group proposed a revision of the criteria of AKI and redefined AKI as an absolute increase in serum creatinine level of $\geqslant$ 0.3 mg/dL, or an increase in serum creatinine level > 1.5 times from baseline, or a reduction in urine output < 0.5 mL/kg per hour for > 6 h[1]. AKI that develops in patients with decompensated cirrhosis can be triggered by volume depletion, infection or nephrotoxic acute tubular necrosis, primary renal parenchymal diseases, obstructive nephropathy and hepatorenal syndrome (HRS).

Since the first definition and the diagnostic criteria of HRS were established in 1994, HRS has been widely accepted as a reversible functional renal failure[2]. The International Ascites Club met in 2007 and set up a consensus on a new definition, diagnostic criteria and recommendation for the treatment of HRS[2]. HRS is divided into two types: type 1 and type 2 HRS[2,3]. Type 1 HRS is typified by rapid deterioration of renal function as defined by a rising of serum creatinine level to over 2.5 mg/dL in less than 2 wk, and is characteristically presented as AKI[2-5]. Type 2 HRS runs a slower progressive clinical course with a median survival of 6 mo, and is classically associated with refractory ascites[2-5]. Patients with decompensated cirrhosis or acute on chronic liver failure who suffer from type 1 HRS would present with a critical illness, carrying a grave prognosis and having high mortality[5,6]. The consensus emphasized on the potential reversibility of type 1 HRS as a functional renal failure and the role of spontaneous bacterial peritonitis (SBP) as an important precipitating factor of HRS[2,3,5]. Contrasting with a previous consensus, this new definition gives an importance to HRS which was precipitated by SBP without ongoing shock. The panel emphasized that the treatment for HRS should be started early in the clinical course of SBP-precipitated HRS[2,4,5].

Incidences of HRS in patients with decompensated cirrhosis who develop ascites was equal to 18% after 1 year, and could go up to 39% after 5 years[4]. Apart from SBP, bacterial infection with primary sources of infection other than SBP, upper gastrointestinal hemorrhage, large volume paracentesis without albumin administration, and severe acute alcoholic hepatitis have been reported to precipitate type 1 HRS[4,5].

PATHOGENESIS OF HRS

While liver failure in decompensated cirrhosis progresses, splanchnic and peripheral arterial vasodilatation become markedly prominent with the development of hyperdynamic circulation[2,4,5]. Increased local release of vasodilators, especially nitric oxide, is the principal cause of the vasodilatation[2,4,5,7,8]. Proinflammatory cytokines release after the occurrence of SBP aggravates splanchnic and peripheral vasodilatation[3,7,8].

Relative reduction of intravascular pressure from peripheral and splanchnic vasodilatation stimulates renin-angiotensin, aldosterone and sympathetic nervous system, causing the release of systemic and renal vasoconstrictors[2,4,5,7,8]. Intense renal vasoconstriction from vasoconstrictive hormones leads to markedly low renal perfusion and a significant reduction of glomerular filtration rate[5,7-9]. Suboptimal cardiac function as a consequence of impaired systolic and diastolic stimuli responses is an intensifying pathogenic mechanism in decompensated cirrhosis with type 1 HRS[2-5,7-9].

TREATMENT OF TYPE 1 HRS

Liver transplantation is the definite treatment for type 1 and type 2 HRS[3]. From a recent retrospective study in decompensated cirrhotic patients with type 1 HRS who underwent liver transplantation, type 1 HRS resolved in 75.8% of patients after transplantation[10]. The predictor of HRS non-reversal at post-liver transplant was the duration of pre-transplant dialysis[10]. However, because of scarcity of liver grafts and the complexity of patient conditions, the first line treatment of type 1 HRS, which should be considered, are vasoconstrictors plus albumin infusion[2,4,5,7,8]. Vasoconstrictors such as terlipressin help to improve hepatic and renal hemodynamics, decreasing hepatic venous pressure gradient and portal venous blood flow, and raising mean arterial pressure[11]. Terlipressin should be initiated at 0.5-1 mg every 4-6 h[9]. The dose of terlipressin can be increased every 2 d if there is no clinical response, to a maximum of 12 mg/d[2,5]. Terlipressin should be discontinued if there is no response seen for reduction of serum creatinine level after 3 d[2,5]. Treatment duration should be expanded until type 1 HRS resolves, or having received the combined treatment for a maximum of 14 d[2,5]. Albumin should be started at 1 g/kg on the

first day, and the dose can be increased to a maximum of 100 g if there is no or inadequate clinical response, followed by 20-40 g/d on the following days[2,5]. From a previous study, the complete response rate could reach 60% in patients with type 1 HRS after the combined pharmacotherapy[2]. The renal dysfunction was reversible in 34%-60% of patients and the recovery of renal function was sustainable in 70%-80% of patients after the treatment was discontinued[4,12-14]. After the completed treatment of terlipressin and albumin, type 1 HRS rarely recurs, if it is reversal[15]. Baseline serum levels of creatinine < 5 mg/dL and bilirubin < 10 mg/dL, and an increase mean arterial pressure ⩾ 5 mmHg on day 3 are predictive factors of good response to terlipressin and albumin[15-18]. From the results of meta-analysis studies, besides the benefit in HRS reversal, the combined treatment is helpful in reducing mortality[13,19]. A meta-analysis showed that the treatment of type 1 HRS with terlipressin led to increased incidence of cardiovascular events including cardiac arrhythmia, myocardial ischemia, intestinal infarction and hypertension comparing to the control groups (14% *vs* 0%)[13]. When terlipressin was compared with other vasoconstrictor drugs such as norepinephrine, there was no difference in term of the efficacy in HRS reversal between both drugs[14,20,21]. However, adverse events during the course of type 1 HRS treatment were less often seen in the type 1 HRS patients who were treated with norepinephrine[20,21]. The cost of norepinephrine is cheaper than terlipressin, but the drug requires continuous intravenous infusion under close monitoring of vital signs in intensive care units. A recent randomized controlled trial revealed that terlipressin plus albumin was more effective in HRS reversal than midodrine and octreotide plus albumin[22].

PREVENTION OF TYPE 1 HRS

In decompensated cirrhotic patients who developed SBP, albumin infusion (1.5 g/kg at the first diagnosis of infection together with 1 g/kg at 48 h later), comparing to a control group, can decrease the development of type 1 HRS (10% *vs* 33%) and hospital mortality (10% *vs* 29%)[5,23]. For type 1 HRS with ongoing infection, treatment with antibiotics alone can reverse type 1 HRS in only 33% of treated patients[24]. The patients who did not have HRS reversal were associated with poorer prognosis and higher mortality than those who were in the treatment response group[24]. Thus, for type 1 HRS precipitated by infection, early management with vasoconstrictors plus albumin infusion along with antibiotics tends to be more useful and logical than treatment with antibiotics alone. A proof of concept study was recently reported[25]. Early treatment with terlipressin and albumin is effective and safe in type 1 HRS patients with sepsis[25,26]. Renal improvement is seen in two-thirds of decompensated cirrhotic patients with sepsis and type 1 HRS after the combined treatment of terlipressin and albumin[25].

For cirrhosis with infection with primary sources other than SBP, albumin infusion in combination with antibiotics have more advantages in improving renal and circulatory function than using antibiotics alone[27]. The use of albumin infusion in patients with infection other than SBP tended to reduce the incidences of HRS and improve survival[27].

Antibiotic prophylaxis in decompensated cirrhosis with upper gastrointestinal bleeding was showed to reduce bacterial infection and mortality[8]. Albumin replacement (8 g per 1 liter of ascites removal) after large volume paracentesis prevents renal and electrolyte impairment and the activation of endogenous vasoactive hormones[28,29]. The use of pentoxifylline in severe acute alcoholic hepatitis is useful in reducing renal dysfunction and type 1 HRS[8].

CONCLUSION

Type 1 HRS is a critical condition affecting patients with decompensated cirrhosis. It is an infrequent event, but has a grave prognosis. Management of type 1 HRS requires very rapid diagnosis according to the consensus criteria of the International Ascites Club (2007) and exclusion of other causes of AKI. The role of renal biomarkers for early diagnosis of type 1 HRS is currently under investigation. Unless the diagnosis of type 1 HRS is made promptly and the combined treatment of albumin and vasconstrictors is started quickly, the complete response of acute renal dysfunction may not be achieved, and poor outcomes with high mortality can be the consequences. The advantage of early treatment of vasoconstrictors plus albumin is fully supported from the study of sepsis-related type 1 HRS. Until now, data has not confirmed the benefits of terlipressin over norepinephrine or other vasoconstrictive drugs. The choice of vasoconstrictors depends on the suitability and availability of the medications and medical facilities.

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