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DIAGNOSTIC AND TREATMENT OPTIONS OF HEPATORENAL SYNDROME IN CIRRHOSIS

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ABSTRACT

Hepatorenal syndrome (HRS) is a serious complication in patients with advanced cirrhosis and ascites, having marked circulatory dysfunction and acute liver failure. The most effective treatment option for HRS is liver transplantation. Patients with type 1 HRS generally have a fatal outcome without expedited liver transplantation. Also newer treatments such as combination of vasoconstrictor plus albumin, TIPS and MARS help in the effective management of renal function in patients with HRS. Among these, the combination therapy improves the survival in patients with type 1 HRS. CRRT and MARS in selected patients is life saving while waiting for OLT. Thus these newer therapeutic approaches have improved the management of HRS in cirrhosis patients.

KEYWORDS*:* Hepatorenal syndrome, cirrhosis, AKI in liver disease, functional renal failure in liver disease, OLT, vasoconstrictors, TIPS.

Abbreviations: HRS, hepatorenal syndrome; OLT, orthotopic liver transplantation; TIPS, transjugular intrahepatic portosystemic shunts; MARS, molecular adsorbent and recirculating system; CRRT, continuous renal replacement therapy; IAC, international ascites club.

INTRODUCTION

During 19th century the occurrence of kidney failure was first described in patients with cirrhosis, but the term hepatorenal syndrome (HRS) was first used in 1932 by Helvig and Schutz. Later on, it was used to describe any type of simultaneous severe renal and hepatic impairment. In the middle of the century, it was clear that renal failure was functional in

advanced liver disease. Further the studies showed that functional renal failure in liver disease may be of 2 forms: a more frequent, easily reversible, and less severe due to vascular under filling and a more severe due to intense renal vasoconstriction. Thus the term was restricted to the most severe form of pre-renal failure in the course of advanced liver disease.[1] HRS is progressively increasing serum creatinine in advanced liver failure patients. It's observed in patients jointly with liver failure and portal hypertension.[2]

HRS is the most severe complication in patients with cirrhosis and is defined as renal failure emerging in liver disease when all other causes of renal failure are excluded.[3] The International Ascites Club (IAC) defined HRS as: "a syndrome that occurs in patients with advanced chronic liver disease and advanced hepatic failure and portal hypertension characterized by impaired renal function and marked abnormalities in the arterial circulation and activity of the endogenous vasoactive systems. In the kidney there is marked renal vasoconstriction that results in low glomerular filtration rate (GFR). In the extra renal circulation, there is a predominance of arterial vasodilation that results in reduction of total systemic vascular resistance and arterial hypotension."[4]

HRS was first classified into 2 groups: Type 1 and Type 2, by the IAC in 1994. [5, 6, 7]

Type 1 HRS occurs following a precipitating factor such as spontaneous bacterial peritonitis (SBP), which is the most important factor for HRS. [8-11] Type 2 usually arises as a result of refractory ascites.

Type I HRS	**Type II HRS**
Rapid deterioration in renal function.	Renal impairment less rapidly
Doubling of the initial serum creatinine >2.5 mg/dl or 50% reduction in 24 hr creatinine clearance to < 20 ml/min in <2 wks.	Serum creatinine level >1.5 mg/dl and associated with sodium retention.
Survival in the order of weeks.	Survival time measured in months.

Diagnosis: The diagnosis has been defined in two IAC consensus conferences in 1996 and in 2005.

Table 2: IAC diagnostic criteria for HRS.[12]

Cirrhosis with ascites
Serum creatinine >1.5 mg/dl
No improvement of serum creatinine (decrease to <1.5mg/dl) after 2 days off diuretics and volume expansion with albumin (1g/kg/d up to a maximum of 100g/d).
Absence of shock
No current or recent treatment with nephrotoxic drugs.

Absence of signs of proteinuria (> 500 mg/d) or hematuria (>50 RBCs per high-power field) or abnormal renal ultrasonography.

Additional criteria for further supportive evidence [13]

Urine volume	< 500 ml/day
Urine sodium	< 10 mEq/l
Urine osmolarity	>Plasma osmolarity
Urine RBC	< 50 / high power field
Serum sodium	< 130 mEq/l

Before diagnosis of HRS, it's important to exclude hypovolemia, nephrotoxic drugs and presence of intrinsic renal disease. According to the modified classification of renal failure in cirrhotic, given by a working party, type 1 HRS may be considered as a form of AKI in cirrhotic and type 2 HRS as CKD in cirrhotic. [14] HRS type 1 has very poor prognosis in cirrhotic and predicts a median survival of only 3 months and untreated type 1 HRS has a median survival of about 1 month.[15] Watt et al showed that only 59% of ARF was diagnosed as HRS fulfilling IAC diagnostic criteria. Gines et al. estimated 1yr probability of HRS in patients with cirrhosis at 18% and 5yr probability at 39%.[16] Median survival probability were reported as 1 and 6.7months in patients with type 1 and type 2 HRS respectively.[17]

Management of HRS

Prevention

It's important to avoid the precipitating factors of renal failure in cirrhosis patients. Following are the measures that should reduce the incidence of HRS:

- Prophylactic treatment with antibiotics to prevent SBP in patients who had previous episodes.
- Optimal fluid management.
- Use salt-poor albumin for fluid replacement in patients undergoing large volume paracentesis.
- Use of diuretics with caution.
- Avoid of nephrotoxic drugs (Gentamicin, NSAIDs, and X-ray contrast media).

Non-pharmacological treatment

All the drugs that have been investigated in HRS aims to increase the renal blood flow. This has been either directly by encouraging renal vasodilation or indirectly by splanchnic

vasoconstriction. Drugs which spill over into systemic circulation may actually exacerbate the intense vasoconstriction already present. [18]

1) Liver Transplantation (OLT)

Orthotopic Liver Transplantation remains the best treatment for suitable candidates with HRS as it offers a cure of both liver and kidney failure. Overall long term survival of 65% has been reported after OLT. Patients with HRS have high risk of post surgical morbidity, early mortality and longer hospitalization. Gonwa et al reported that at least one third of patients require hemodialysis post operatively and 5% requiring long term hemodialysis. Renal dysfunction is common in the first few days after transplantation. However, GFR gradually improves by the sixth postoperative week. The systemic and neurohumoral abnormality associated with HRS also resolves in the first postoperative month. Long term survival rates are excellent (60%) in transplanted HRS patients, but slightly lower than 70-80% survival rates in non-HRS transplants. Also it's better than survival rate of HRS patients not receiving transplants (0% at 3yrs).

Table 3: Therapeutic modalities used in HRS

Therapeutic modality	Studies	Improved renal function	Improved survival
Terlipressin + albumin	RCT and meta-analysis	yes	Yes
Noradrenaline + albumin	RCT	Yes	? Yes
Midodrine + Octreotide + albumin	Single small RCT	Yes	No
TIPS	Non-RCT	Yes	No
Albumin dialysis	Small RCT	Yes	No
OLT		Yes	Yes

2) Peritoneovenous shunting (PVS)

PVS seems attractive in theory as it leads to plasma volume expansion and improvement of circulatory function. However, only very few studies evaluated the role of PVS as it was mainly used for treating refractory ascites. This may be important for type 2 HRS patients, who often develop refractory ascites, are not the candidates for OLT and do not tolerate frequent large volume paracentesis. PVS has no role in type 1 HRS. [19]

3) Transjugular Intrahepatic Portosystemic Shunts (TIPS)

TIPS have been used to control portal hypertension and HRS. Many patients with advanced liver disease with renal failure have contraindications for TIPS. The mechanism by which it

exerts this effect might be the result of reduced portal pressure, hepatorenal reflex suppression, improved circulating volume or amelioration of cardiac function. Guevara et al. prospectively investigated the biochemical, hemodynamic and neurohumoral changes post TIPS in 7 type 1 HRS patients. Renal function was improved in 6 patients (86%) after one month. Patient's survival ranges from 10 to 570-d and 30-d survival in 5 patients (71%). Among 41 patients, TIPS improved the creatinine clearance, urinary sodium and one yr survival of 48%.[20] A recent prospective study by Wong et al. found that there was persistent improvement in serum creatinine, renal blood flow, GFR, and natriuresis after TIPS insertion. Also plasma renin and aldosterone levels were reduced 1 month after TIPS. 5 patients from 14 who received combined therapy with oral midodrine and IV octreotide with albumin infusion was alive 6-30 months after TIPS, with only one patient requiring OLT 13 months afterward. This study suggests that combination therapy may preclude the need for future OLT and improve survival compared with vasoconstrictor therapy alone.[21] Likewise, a beneficial effect of combination therapy was observed in 11 patients who had type 2 HRS and were treated with sequential terlipressin and TIPS insertion. The results were very encouraging and require future prospective assessment.

4) *Albumin Dialysis:* Albumin dialysis is supposed to act on the principle of removing albumin bound toxins, which in case of HRS would be cytokines and vasodilators. In a small RCT among 13 patients with type 1 HRS, there was a significant improvement in renal function and short term mortality in patients undergoing molecular adsorbent and recirculating system (MARS) therapy. The MARS is a cell free, modified dialysis technique which removes both albumin bound and water soluble substances by using a combination of albumin enriched dialysate and CRRT. The advantage of using MARS in HRS relies on the assumption that removing albumin bound toxins (e.g.: bile acids), which have a detrimental effect on hepatocytes and other organs, including the kidney, will stabilize liver function and improve other end organ damage.

Pharmacological treatment: Although only a few controlled trials have been conducted, the results so far are encouraging and suggest an increased role for medical therapy, given the current shortage of donor pool in the face of an ever-increasing demand for organs.

1) *Systemic Vasoconstrictors*

Systemic vasoconstrictors are the most promising pharmacologic agents in the management of HRS. They rely on the assumption that interrupting the splanchnic vasodilation will

subsequently relieve the intense renal vasoconstriction. Vasoconstrictors studied include vasopressin analogues (octapressin, ornipressin and terlipressin), somatostatin analogues (Octreotide), and the α-adrenergic agonists (midodrine and norepinephrine).

- ***Vasopressin analogues***

Splanchnic vasoconstrictor therapy aimed at reversing hyper dynamic circulation and increasing the central blood volume, appears promising. Vasopressin-1 receptor agonists such as *octapressin, ornipressin* and *terlipressin* act as preferential splanchnic vasoconstrictors and redistribute blood to the central circulation. These agents reverse the over activity of the sympathetic nervous system and RAAS, and stimulate ANP release.

Octapressin, a synthetic vasopressin analogue was first used in 1970 to treat type 1 HRS. Renal plasma flow (RPF) and the GFR improved in all patients, all of them subsequently died from sepsis, gastrointestinal bleeding and liver failure. Because of these discouraging results, the use of Ornipressin attracted attention. Three important studies by Lenz and colleagues demonstrated that short-term use of ornipressin resulted in an improvement in circulatory function and a significant increase in RPF and GFR. The combination of Ornipressin and albumin was subsequently tried by Guevera in patients with HRS. Treatment had to be discontinued in 4 patients after fewer than 9 days because of the ornipressin complications (ischemic colitis, tongue ischemia, glossitis). Although a marked improvement in the serum creatinine level was observed during the treatment, but renal function was deteriorated on withdrawal. In the remaining 4 patients, improvement in RPF and GFR was significant and was associated with reduction in serum creatinine. These patients subsequently died, but there was no recurrence of HRS.

Due to higher incidence of severe adverse effects with ornipressin, the same investigators used terlipressin (with fewer ADR). In this study, patients were treated with terlipressin and albumin for 5-15 days. This was associated with marked reduction in serum creatinine and improves mean arterial pressure. Reversal of HRS was noted in 7 of 9 patients and HRS did not recur when treatment was discontinued. No ischemic adverse effects were reported and the study showed that terlipressin with albumin is safer and effective for the treatment of HRS. When used in conjunction with albumin, improvement in GFR and reduction in serum creatinine occur in 60-75% of type 1 HRS patients. Repeated course of terlipressin with albumin was more effective than intermittent therapy.[22]

- ***Somatostatin analogue***

Octreotide is a synthetic derivative of somatostatin. It's a potent physiological inhibitor of several gastrointestinal functions, one of which is the reduction in intestinal blood flow by splanchnic vasoconstriction. The data on its use in HRS were limited to recent publications by Angeli et al. and Kaffy et al. (five patients with alcoholic cirrhosis). Octreotide alone is not more effective than placebo [23] and did not improve serum creatinine. Experimental studies showing that octreotide potentiate the effect of vasoconstrictors would suggest the latter. [24]

- ***α-Adrenergic agonists***

In 1956, Hecker and Sherlock used norepinephrine to treat cirrhotic patients with HRS, which act by improving in arterial pressure and urine output. However there was no improvement in biochemical parameters of renal function and all patients subsequently died. *Noradrenaline* infusion (dose 0.5 to 3 mg/hour) along with albumin has the same effectiveness as terlipressin plus albumin in improving renal function and circulatory function in HRS patients. Another larger open label RCT from India, demonstrated similar improvement in renal functions and survival rates in the two groups (noradrenalin + albumin vs. terlipressin + albumin).

Midodrine is another vasoconstrictor used in patients with HRS. Midodrine was used in a dose 2.5 to 12.5mg PO Q8H combined with octreotide 100µg subcutaneously Q8H in 5 patients with type 1 HRS. These were compared with 8 patients with standard therapy. Both groups received albumin (50-100 ml daily). Patients with combination therapy had HRS reversal with increased in GFR and reduced renin activity. There were no ischemic side effects. Angeli et al showed that long-term administration of midodrine and octreotide improve renal function in 8 type 1 HRS patients. A study of 14 patients by Wong et al reported improvement in renal function in patients in 10 patients. Three of these patients subsequently underwent liver transplantation.

2) Renal vasoconstrictor antagonists

Saralasin, an antagonist of angiotensin II receptor was used first in 1979 to reverse renal vasoconstriction. This drug inhibit the homeostatic response to hypotension seen in cirrhotic and led to the worsening of hypotension, thus deteriorates renal function. Poor results were observed with *phentolamine* an alpha-adrenergic antagonist, highlighting the importance of SNS in maintaining renal hemodynamic in HRS patients.

Endothelin, a potent endogenous vasoconstrictor, can be used in patients with hepatorenal syndrome. A case series by Soper et al reported an improvement in the GFR in 3 patients with cirrhosis, ascites and HRS who received an antagonist of endothelin A receptor. All 3 patients showed a dose-response improvement in inulin and para-aminohippurate excretion, RPF, and the GFR in the absence of changes in systemic hemodynamics. These 3 patients were not candidates for OLT and subsequently died. More work is needed to explore this therapeutic approach as a bridge to transplantation.

3) Renal vasodilators

- ***Prostaglandin analogues***

Misoprostol, a synthetic analogue of PGE1 would potentially act on renal circulation as a vasodilator and its use in HRS was examined by Fevery et al in 1990. Four patients with HRS received misoprostol (0.4mg 4 times oral). All 4 patients responded with a diuresis and a fall in creatinine, although only two patients had natriuresis. Three patients were died in days 10, 30, 40 of bleeding, encephalopathy and pneumonia, respectively; the fourth patient underwent liver transplantation. Gines et al. studied nine patients with renal impairment and/or hyponatraemia, were given 200µg misoprostol every 6h for 4 days. There were no change in GFR, sodium excretion, and free water clearance. An infusion of PGE2 in further, similar group of nine patients had similarly disappointing - lack of effect on GFR and sodium excretion, and significantly decrease free water clearance.

- ***Dopamine***

Dopamine was frequently prescribed; there was no evidence of effectiveness as monotherapy in the treatment of HRS. Low-dose dopamine (<5µg/kg/h) infusion increases RPF and GFR in normal subjects, but despite improved RPF in cirrhotic with renal impairment there is no effect on GFR or outcome. Combination of dopamine and noradrenalin led to recovery from HRS in a single case [25]. There have been 5 studies examining the use of dopamine in HRS in which it was unable to identify any benefit of combined dopamine and PGA1 infusion in four patients with HRS. Bennett et al. examined RPF in 12 decompensate cirrhotic (seven had HRS), using xenon 133 washout technique during an intra-arterial infusion of suppressor doses of dopamine. In the patients with HRS, dopamine appeared to improve the angiographic appearance of renal cortical vasculature, and cortical blood flow. No change was seen in GFR or urine output within 12 ± 24 h infusions.

4) *Antioxidant therapy:* There has been one series of 12 patients (nine had alcoholic cirrhosis) with HRS where N-acetylcysteine was used as an antioxidant. This treatment was well tolerated with no side effects. At baseline, following aggressive fluid replacement, the mean creatinine clearance was 24±3 ml/min raised to 43±4 ml/min following five days of therapy. This was associated with an increase in urine output and sodium excretion from 1.2±0.5 to 1.8± 0.6mmol/h (P<0/05). High survival figures of 67% at one month and 58% at 3 months were observed. This includes two patients who underwent successful OLT after renal function improvement. Information on etiology of the patient's liver disease in the patients who survived was not provided. [26]

5) *Pentoxifylline:* Meta-analysis showed that pentoxifylline reduces the hepatic-related mortality due to HRS, but trial sequential analysis did not support this result. Data from one trial suggests that pentoxifylline may increase the occurrence of serious and non-serious adverse events compared to control.[27]

CONCLUSION

The most recent advancements in the pathophysiology of HRS are the basis of all new therapeutic interventions. Liver transplantation is the best option for HRS, but is seldom applicable. The combination therapies are now found to have more promising survival in patients with HRS. Therapy with terlipressin and albumin looks most promising, but there is a paucity of data to confirm the results. Use of vasoconstrictors and TIPS remain experimental and also requires further studies. However, all the pharmacological options require further more studies to prove its clinical usefulness.

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