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A critical review on the recent developments on hepatorenal syndrome

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Abstract
Hepatorenal syndrome (HRS) is a life-threatening complication of AKI in liver cirrhosis. It is a type of functional renal failure occurring due to the progression of splanchnic vasodilation in patients with liver cirrhosis, end-stage liver failure and occasionally in fulminant hepatitis. Initially, HRS was classified as type 1 HRS and type 2 HRS, but nowadays the International Club of Ascites (ICA) has revised the definition and classification of HRS based on pathophysiological characteristics and clinical scenario as HRS AKI and Non-HRS AKI, which differentiates AKI based on the evidence of any intrinsic renal disease or presence of nephrotoxic agents. Cardiac arrhythmias, endotoxemia and refractory ascites contribute to low survival rate and hence increases the risk in HRS. Early diagnosis is the key strategy for successful management of HRS. The goal of HRS management is the reversal of the syndrome by prompt identification and management of underlying cause and to correct hemodynamic instabilities by volume expanders. Management of HRS includes a combination of vasopressor therapy with plasma expanders like albumin which accounts for almost 80 % of survival rate in responders to the treatment. Recent studies suggest non-pharmacological prevention of HRS with the use of a combination of green tea extract with a probiotic mixture for fighting against the high oxidative stress and endotoxemia in HRS.

Keywords: hepatorenal syndrome, cirrhosis, international club of ascites, acute kidney injury, HRS-AKI

Introduction

Hepatorenal syndrome is a common problem in patients with advanced cirrhosis and ascites. It is a functional type renal failure which occurs in a setting of circulatory dysfunction such as increased splanchnic blood flow, hemodynamic alteration in the arterial circulation, activation of vasoconstrictor systems and extreme renal vasoconstriction which leads to reduced renal perfusion and GFR [1, 2]. HRS severely reduces the ability of kidneys to excrete sodium and water, thus most of the patients present with dilutional hyponatremia. HRS may develop spontaneously or could be accelerated due to certain precipitating factors like alcohol intake, hepatitis viruses, AIH flare and extra hepatic factors like bacterial infection/translocation, sepsis, variceal and non- variceal bleeding [3].

In recent years it has been recognized that the HRS is not just the functional type syndrome with hemodynamic derangements, but the systemic inflammation, oxidative stress, bile salt related tubular injury also plays a crucial role in the development of AKI. Acute kidney injury is one of the most relevant complications in 20-50% of patients with advanced cirrhosis hospitalized for decompensation. So it is important to mitigate the impact of AKI in terms of morbidity and mortality. Apparently it is also evident that the systemic inflammation which leads to organ failure and acute decompensation in advanced liver cirrhosis is induced either by pathogen associated molecular patterns (PAMPS) and damage associated molecular patterns (DAMPS). Decompensated liver cirrhosis is the acute worsening in liver function in patients with cirrhosis, characterized by jaundice, ascites, encephalopathy, variceal hemorrhage and hepatorenal syndrome. Almost 10% of cirrhosis develops into HRS [2, 4, 5].

Methodology

Literature search was conducted in Pubmed to identify relevant articles pertaining to the research question. Studies published in Pubmed till April 2020 corresponding to the search criteria were included for consideration. Article search was conducted to identify original research publications addressing the diagnosis and management of HRS. The search terms used were: Hepatorenal syndrome AND diagnosis OR treatment OR classification OR pharmacological treatment OR surgical OR non pharmacological treatment. Only articles published in English language was considered. Letters to editors, narrative reviews and information presented at conferences were excluded from consideration. Once all the relevant articles were extracted, relevant studies addressing the recent development in the diagnosis and management of HRS were selected.

Incidence

In about 25-50% of patients hospitalized with cirrhosis have AKI after an episode of acute decompensation [6]. Incidence of Hepatorenal syndrome development is 5% in patients with chronic liver disease who present with upper gastrointestinal bleeding, 30% of patients hospitalized with spontaneous bacterial peritonitis, and 10% of patients with ascites treated with total paracentesis, and 25% of patients with severe alcoholic hepatitis. The probability of hepatorenal syndrome developing in a patient having cirrhosis and new onset of ascites is 7–10%. The 5-year

probability of hepatorenal syndrome developing in a patient with cirrhosis and recurrent ascites is 40% [7].

Classification of HRS

The older classification of HRS (i.e. Type 1 HRS and Type 2 HRS) was predominantly based on the serum creatinine and not on pathophysiology and etiology. Type 1 HRS (HRS-AKI) is described as a rapid progressive deterioration of renal function probably due to a precipitating event with doubling of initial serum creatinine (>2.5mg/dl or 220µmol/l) in 2 weeks duration. Type 2 HRS (HRS-CKD) is a steady or slowly progressive renal dysfunction accompanied with refractory ascites without a precipitant (serum creatinine >1.5mg/dl or 133µmol/l) [2].

International Club of Ascites has proposed a newer classification for hepatorenal syndrome based on the pathophysiological characters i.e. HRS AKI and Non-HRS AKI. The time limit of 2 weeks to diagnose HRS-1 and the limiting threshold of Sr. creatinine levels (i.e.2.5mg/dl) were removed in newer classification.

HRS-AKI is described as worsening of kidney function in individuals with advanced cirrhosis with an absolute increase in serum creatinine ≥0.3 mg/dl within 48h and/or urinary output ≤0.5ml/kg body weight ≥6h or percent increase in serum creatinine≥50% using the last available outpatient serum creatinine within 3 months.

Non-HRS AKI (HRS-NAKI) describes the grounds of AKI in cirrhotic patients such as bile acid nephropathy, pre renal hypovolemia due to excessive fluid and blood loss or excessive use of diuretics, or presence of any other nephrotoxic agents, acute tubular injury, acute interstitial nephritis, acute tubular necrosis [6]. The criterion for diagnosis of HRS-NAKI is based on initial presentation. HRS-NAKI is further classified into HRS-AKD and HRS-CKD. HRS-AKD is the percent increase in serum creatinine<50% or an eGFR <60ml/min/1.73m^2 for <3months in the absence of other structural causes. HRS-CKD is described as eGFR<60ml/min/1.73m^2 for > 3months in the absence of other causes [2].

Pathophysiology

Classic peripheral arterial vasodilation hypothesis

Renal dysfunction in cirrhosis: According to the peripheral arterial vasodilation hypothesis, HRS is a life-threatening manifestation of splanchnic vasodilation caused by the portal hypertension in cirrhosis. Increase in the portal hypertension causes shear stress in the portal blood vessels, causing the release of local vasodilators like nitric oxide and prostanoids from endothelium. This in turn causes arterial hypotension and leads to the activation of baroreceptors, stimulation of sympathetic nervous system and the RAAS pathway to compensate these hemodynamic changes by increasing the cardiac output and heart rate. Despite these changes, local endothelin secretion and vasopressin release reduces the intraglomerular blood flow. Thus aldosterone and vasopressin leads to sodium and water retention initiating ascites formation. At this phase, arterial pressure is severely dependent on vascular effect of the sympathetic nervous system, angiotensin 2 and vasopressin. Interestingly, splanchnic circulation is resistant to the effect of angiotensin 2 and vasopressin due to the local rise of nitric oxide and prostanoids. Thus arterial pressure is preserved by vasoconstriction of the extrasplanchnic vascular territory (kidney, muscle, skin), leading to the renal vasoconstriction and decrease in renal perfusion, GFR, azotemia. This contributes to the final phase of cirrhosis, i.e. the hepatorenal syndrome [6, 8].

Cardiac dysfunction in HRS

The normal response to manage the arterial hypotension is the release of angiotensin 2, activation of sympathetic nervous system, which not only causes vasoconstriction but also increases cardiac output, ventricular contractility, heart rate, showing an abnormal cardiac response to preserve renal blood flow in such patients. But in most advanced stages of cirrhosis, these measures are no longer helpful to preserve kidney perfusion from extreme renal vasoconstriction causing decrease in GFR, hypertrophy of cardiac chambers and changes in cardiac electrophysiology occurs in response to stress stimuli [6, 9]. This is common in cirrhotic cardiomyopathy. However, in Type-2 HRS a decrease in the cardiac output is observed, indicating impairment in cardiac inotropic and chronotropic functions [8].

Diagnosis

Patients with HRS have high short-term mortality. Early diagnosis and initiation of therapeutic management is the key for better patient outcome.

Diagnostic criteria for HRS as per International Club of Ascites (ICA) includes:

Presence of cirrhosis and ascites

Diagnose AKI based on the ICA-AKI criteria, it includes:

a. Baseline Sr. Creatinine value should be obtained i.e, a value obtained 3 months prior hospital admission(in case of more than 1 value choose the value closest to the time of hospital admission) or the value of Sr. Creatinine upon admission in patients without a previous Sr. Creatinine value should be obtained.
b. Definition of AKI: increase in Sr. creatinine ≥0.3mg/dl within 48hr or a percentage increase in sr. creatinine (50 %) from the baseline value.
c. Staging of AKI :

1. Stage 1: serum Creatinine ≥0.3mg/dl or an increase in Sr. creatinine >1.5 fold to 2 fold from baseline.
2. Stage 2: An increase in Sr. creatinine > 2fold to 3 fold from baseline.
3. Stage 3: An increase in Sr. creatinine > 3fold from baseline or Sr. Creatinine ≥0.4mg/dl.

a. Progression of AKI:
b. Progression of AKI to a higher stage or need for RRT, or Regression of AKI to lower stage.
c. Response to treatment:

1. No response: defined as no improvement of AKI despite treatment
2. Partial response: defined as an improvement in the AKI stage with a reduction of serum creatinine by more than or equal to 0.3mg/dl (26.5µmol/l) from the baseline value.
3. Full response: Return of Sr. creatinine to the baseline value (within 0.3mg/dl)

a. No response after 2 consecutive days of diuretic withdrawal and plasma volume expansion with albumin 1g/kg.
b. g. Absence of shock and no current or recent use of nephrotoxic drugs

c. h. No macroscopic signs of kidney injury (no proteinuria, micro-hematuria, or findings on renal ultrasonography [1].

Urinary Neutrophil Gelatinase-Associated Lipocalin (ungal)

NGAL, also known as lipocalin-2, is a protein present in neutrophils which are released at low levels from the kidney (loop of Henle and collecting ducts). As the molecule is small in size and protease-resistant it is released predominantly through urine during kidney injury. u-NGAL can be used successfully as a potent early diagnostic biomarker in AKI. Turbidimetric particle-enhanced immunoassay cab be used for quantitative determination of NGAL in human urine. This is a more sensitive indicator of kidney injury compared to creatinine value, as uNGAL level will rise within 2hrs of kidney injury (i.e. before creatinine, which takes almost 24-72 h). As per the study conducted in Korea, u-NGAL has the highest accuracy compared to urinary IL-18 and other conventional biomarkers and also helps in differential diagnosis i.e. it differs greatly based on the cause of AKI such as PRA (prerenal azotemia), HRS and ATN in cirrhotic patients. Thus it can be used as an independent prognostic factor in HRS patients [10, 11]. Cut-off value for urinary NGAL: - Up to 107ng/mL in adults and 117.6ng/mL in pediatrics.

Cystatin C

Cystatin is relatively small and low molecular weight protein produced by all nucleated cells in the body. It is extensively used as a biomarker to assess kidney function. It is constantly filtered from the blood by glomeruli. From the filtrate fluid the kidneys reabsorb Cystatin C and break down them, thus an increase in Cystatin C level in urine indicates low glomerular filtration rate. Cystatin C is a more sensitive, accurate and reliable biomarker compared to creatinine as it gives a better estimation of GFR and is independent of gender, muscle mass, inflammation and malignancy [11, 12]. Cut-off concentration of Cystatin C is 1.0mg/l

Cell cycle arrest biomarkers

KI is usually caused due to ischemic reperfusion injury (IRI). After an ischemic injury, epithelial cells of proximal convoluted tubule are more susceptible to injury due to the release of reactive oxygen radicals. The proximal tubular epithelial cells (PTCs) has a great inherent capability to regenerate from the injury. Sustained ischemic injury to PTCs (severe AKI) can cause the cells to arrest the cycle in G1/S or G2/M phase guides to 1. maladaptive repair and fibrotic outcome (interstitial fibrosis). The arrest in the cell cycle is cardinally due to DNA damage, reactive oxygen species, cytokine signalling via nuclear factor kappa beta (NF-κβ) and p38 mitogen-activated protein kinase (p38-MAPK) pathways [13].

There are 2 types of independent cell cycle arrest biomarkers:-

a. Tissue metalloproteinase inhibitor 2 (TIMP2)
b. Insulin-like growth factor-binding protein 7 (IGFBP7)

The concept behind an increase in the level of these biomarkers is that renal ischemia or nephrotoxic drugs can up-regulate the p21 expression, which is a potent cyclin kinase inhibitor. Cell cycle inhibitory effects are exerted by TIMP-2 and IGFBP7. Thus there will be increased excretion these proteins due to progressive 5 tubular cell depletion. Even though there is increased excretion of TIMP-2 and IGFBP7, there is no change in renal cortical/medullary TIMP-2, IGFBP7 mRNAs, which implies there is no gene transcription.

Although these markers are not completely reliable as there will be an increase in the production of plasma TIMP-2 and IGFBP7 concentrations due to extra-renal tissue injuries. This can elevate the filtrate load in glomeruli and thus its urinary excretion [14]. Cut off value for TIMP-2x IGFBP7 for AKI 0.3-2.0 (ng/mL) ²/1000.

POCE and Misclassification of AKI and HRS

Despite the ICA-AKI criteria for the diagnosis of HRS, approximately 30-60% of patients with cirrhosis and AKI are misdiagnosed as HRS-1. Therefore there must be an improved diagnostic approach for HRS.

It has been given in ICA-AKI criteria that cirrhotic patients who developed AKI should undergo a standard treatment of diuretic withdrawal and 2hrs of volume expansion with IV albumin of dose 1mg/kg. This is to ensure that AKI is caused due to volume depletion. Remarkably albumin-based volume expansion is done without checking the patient's volemia i.e. arterial blood volume, central venous pressure or echocardiography. As a consequence, such an approach may lead to risk for iatrogenic fluid overload or insufficient volume repletion. Point of care echocardiography (POCE) can be used as a consistent tool for assessing volume and hemodynamic status in hospitalized patients. The inferior vena cava collapsibility index (IVCCI) and inferior vena cava diameter (IVCD) parameters can be successfully used as a non-invasive measure to evaluate CVP and fluid responsiveness.

Failure to assess volemia in cirrhosis and ascites patients with AKI may lead to high-risk complications like hypovolemia or hypervolemia, which may lead to high output heart failure, sodium retention and Porto-pulmonary hypertension as volume repletion measure makes them vulnerable to hemodynamic alterations.

Treatment for patients with hemodynamic instability and those categorized according to POCE are as follows:

1. In patients who are fluid depleted and responds to albumin therapy, 1mg/kg/day IV albumin, maximum- 100g/day given as 25g every 5-6 hrs.
2. In patients with fluid overload or fluid expansion, Furosemide 60-180mg every 8-12hr.
3. In patients with intra-abdominal hypertension; LVP (large volume paracentesis) should be considered.

These attempts provide proper diagnosis of HRS-1 and suitable hemodynamic instability management, thus better patients outcomes and early setback of AKI course [15].

Dobutamine Stress Echocardiography

Cardiac dysfunction is an important root cause for HRS development since patients with HRS have high resting cardiac output. A study conducted by Anoop *et al* have concluded that low cardiac reserve is the strongest independent predictor for HRS development, which can be diagnosed with low dose (10µg/kg/min) dobutamine infusion for graded inotropic stimulation combined with echocardiographic imaging of left ventricle

(Dobutamine stress echocardiography). This test is used to assess the myocardial viability, contractile reserve and cardiac physiological response to stress. It was also determined that there

was a 4 fold increase in risk for HRS development in low cardiac reserve patients after adjusting for MELD score [16].

Renal Resistive Index

It is also known as a renal arterial resistive index. It is a non-invasive ultrasonography technique to assess renal arterial resistance, which occurs as a result of vasoconstriction in the progression of cirrhosis to HRS. It is measured using duplex Doppler at the arcuate arteries (at the cortico-medullary junction) or inter-lobar arteries.

Colour and power doppler can be used for accurate diagnosis as it can provide morphological and functional characteristics of intra-parenchymal vascularity and can detect changes in blood flow to the kidney. It is detected using bicolour signals, which differentiates undamaged from damaged or ischemic parts of the kidney.

It can be used for the diagnosis of HRS and as a prognostic factor in liver cirrhosis. It is the ratio of the difference between peak systolic velocity and end-diastolic velocity with peak systolic velocity. The normal range lies between 0.50-0.70 [17].

Mean Arterial Pressure (MAP)

Mean arterial pressure is the arterial pressure applied within the walls of vessels during one cardiac cycle. MAP is influenced by the cardiac output and systemic vascular resistance. MAP helps determine tissue and organ perfusion. It should be maintained at a minimum of 60mmHg. Escalation of MAP can induce nitric oxide release in vascular endothelial cells due to the shearing forces applied on the walls of blood vessels. A decline in MAP leads to Endothelin-1 release, which has an exact opposite mechanism of nitric oxide eventually leading to vasoconstriction and contraction of smooth muscle cells [18].

MAP has an important role in the pathogenesis of HRS. Inappropriate pooling of splanchnic vasodilatation reduces systemic blood pressure and reduces renal blood flow in HRS, thus several studies have detected the subsequent rise in MAP [19] helps in resetting the perfusion pressure back to auto-regulatory range improves renal function.

RAAS pathway aids in maintaining the mean arterial pressure through plasma volume. Reduced perfusion to kidneys affects the renal system and triggers the production of aldosterone, thereby increasing the sodium-water reabsorption and eventually uplifting the plasma volume to normalize mean arterial pressure. The autonomic nervous system helps in regulating MAP through baroreceptors to maintain an ideal MAP range [18].

MAP is calculated using the following formula:

MAP = Diastolic pressure+1/3(Systolic – Diastolic pressure) or MAP = Diastolic+ 1/3(pulse pressure).

The normal arterial pressure lies between 70 mmHg and 100 mmHg [18].

Risk factors

The annual incidence of HRS in cirrhosis patients is around 5% with a very low survival rate. Increased risk for HRS development in patients with cirrhosis includes past episodes of ascites, absence of hepatomegaly and poor nutritional status. As per renal function, urine sodium excretion ≥2mEq/d, free water clearance ≥ 3.3ml/min, serum sodium ≥133mEq/l, serum osmolality >1279 mOsm/kg, urine osmolality >553 mOsm/ kg, serum potassium >4 mEq/L, BUN > 15 mg/dL, serum creatinine >0.9 mg/ dL, and GFR ~80 mL/min. other predictors of HRS include plasma renin activity and plasma norepinephrine.

Among those parameters sodium retention, very low free clearance, dilutional hyponatremia, hypo-osmolality are a cardinal risk factors for developing the hepatorenal syndrome. As per the peripheral arterial vasodilation hypothesis, HRS was considered to be the utmost manifestation of arterial vascular under filling secondary to peripheral arteriolar vasodilation [20].

Endotoxemia

Around 34% of patients with cirrhosis often complaints of renal dysfunction precipitated due to bacterial infections. This is because patients with cirrhosis are predisposed to bacterial infection due to impaired immune response, bacterial translocation due to increased gut permeability, often due to portal hypertension [21].

Enterobacteriaceae, a gram-negative micro-organism, is the major pathogen isolated from patients with HRS. Escherichia coli, Enterobacter species, and Klebsiella pneumonia are the most frequently found organism in cirrhotic and HRS patients, which contributes to high-risk complications such as spontaneous bacterial peritonitis, pneumonia, urinary tract infection and sepsis, high mortality rate, increased economic and clinical burden. The occurrence of Enterobacteriaceae bacteremia usually takes place within 3 months after HRS diagnosis. The patients with high MELD score, post hepatitis cirrhosis B and C, high serum creatinine concentration, uremia, prolonged hospital stay (nosocomial infections) and low MAP contributes to the increased risk for Endobacteriaceae Bacteremia [22].

The major etiology behind endotoxemia in cirrhosis patients include impaired defense barrier in the intestinal mucosa which can cause wide systemic complications. The major integrity of the intestinal lumen is the mechanical barrier which consists of tight gap junctions and IgA, lymphocytes, mesenteric lymph nodes constituting the immune system barrier. The integrity of this barrier gets disrupted causing defects in the immune barrier, leading to reduced IgA level, reduced bile acid release (suppressor of bacterial colonization), loosening of tight junctions leading the bacterial entry into systemic circulation instigating sepsis, multiple organ dysfunction, death.

Due to heavy bacterial translocation, liver undergoes stress, causing ineffective elimination of endotoxins. Also increased expression of TNF-α assist in inhibiting phagocytosis by binding to TNF receptors present in Kupffer cells. Thus dysregulation in Kupffer cells and hepatocytes leads to impaired hepatic clearance of bacterial lipo-polysaccharide, giving them access into systemic circulation [21].

Cardiac Arrhythmias

Despite the higher risk of arrhythmia and atrial fibrillation in cirrhotic patients, hepatorenal syndrome uplifts the risk for arrhythmia due to electrolyte disturbance associated with a decline in renal function. The principal trigger for cirrhotic cardiomyopathy is the conjugated bile acids, which disrupts the ionic channels present in ventricular myocytes which in-turn shortens the action potential duration and impairment in myocardial contractility. The most prominent risk factors for cardiac arrhythmias in cirrhotic patients include age>60, whites,

male, hepatorenal syndrome, jaundice and presence of cardiac risk factors such as IHD, valvular disease, alcoholic, hypertension, obesity and CHF. Prompt identification of reversible risk factors i.e. prevention of hyperbilirubinemia, correction of fluid and electrolyte disturbance, reversal of hepatorenal syndrome, treatment of acute decompensation of ESLD can be helpful in the prevention of cardiac arrhythmia and to decrease the prevalence of the same in ESLD. Use of beta-blockers in prevention of variceal bleeding, spironolactone for volume overload and ascites, decreasing cardiac fibrosis and chronotropy, elevated nitrate levels and decreasing blood pressure and afterload are anti-arrhythmogenic [23].

Management of HRS

Pharmacological management of HRS

The conventional first-line therapy for HRS is a conjunction of vasoconstrictors (i.e. terlipressin) with albumin. The beneficial effects of terlipressin include splanchnic vasoconstriction while improving central vascular territory, increases MAP and decreases RAAS leading to improved GFR and renal perfusion which accounts for reversal of HRS [24]. However, in US combination of octreotide with midodrine is the standard therapy for HRS although it is significantly less effective than terlipressin [25].

Patients with ascites and suspected HRS-1 should be treated by withdrawing diuretic therapy and all other nephrotoxic agents, followed by plasma volume expansion in case of hypovolemia along with proper diagnosis and early eradication of bacterial infection should be done if suspected. In response to the above-mentioned therapy, serum. Creatinine should be monitored closely and identify the early recurrence. If there is no response to above-mentioned therapy, plasma expansion using IV 5% albumin 1g/kg/day for 2 consecutive days should be considered [26].

Role of beta-blockers and Endoscopic Band Ligation

In patients with high-risk varices NSBBs and endoscopic band ligation (EBL) is equally effective. According to Baveno VI guidelines, two major axes for prophylaxis of variceal bleeding are NSBBs and EBL. But studies show there is no change in outcomes for EBL alone or in combination therapy (propranolol + EBL) in terms of mortality and incidence of bleeding [27].

Earlier non-selective beta-blockers (NSBBs) were used to treat portal hypertension (PH). Responses to NSBBs are associated with reduced risk of bleeding, ascites, SBP, HRS and an improved survival rate compared to endoscopy [28]. NSBBs directly reduce the variceal flow and block the occurrence of collateral circulation [27]. Maintaining hepatic venous pressure gradient (HVPG) below 10mmHg reduce the development of large varices, ascites, encephalopathy, variceal bleeding. Beta-blockers can be successfully administered in all patients with no contraindications such as hypotension, chronic bronchial asthma, bradycardia, COPD, uncontrolled diabetes hypoglycemia, cardiac arrhythmias and other conduction abnormalities, thyrotoxicosis, Raynaud's phenomena, heart failure.

Propranolol had proven efficacy in preventing primary and secondary bleeding from varices and portal hypertensive gastropathy. They also reduced bacterial translocation thereby preventing the risk of endotoxemia independent of variceal bleeding. A drawback of BBs was severe hypotension in ascites which interferes with RAAS, thus it was cautioned to avoid in refractory ascites and ESLD.

Carvedilol, an intrinsic α-1 antiadrenergic agent reduces portal hypertension by intra-hepatic vasodilation. It has comparatively superior proven efficacy in reducing HVPG than propranolol and nadolol. At a dose of 6.25-12.5mg/d it significantly reduces PH without producing hypotension and at doses over 25mg/d MAP declines [28]. A meta-analysis showed that EBL with Carvedilol has decreased re-bleeding rates and drug-related adverse events compared to propranolol/nadolol + EBL combination.[5]

Role of potassium-sparing diuretics

Diuretics like aldosterone antagonist and loop are the major stay for patients with ascites in cirrhosis. Spironolactone and Eplerenone are commonly used in ascites. Eplerenone is a steroidal anti-mineralocorticoid, similar to spironolactone which acts by blocking aldosterone, produced due to overactive RAAS and sympathetic system which leads to hyper-aldosteronism in patients with liver cirrhosis and ascites. It selectively binds to recombinant human mineralocorticoid receptor, glucocorticoid, progesterone and androgen receptors than spironolactone. Eplerenone is 40 times less potent than spironolactone and 370 times less potent in inhibiting dihydrotestosterone activation by androgen receptors which account for lesser side effects like gynecomastia, abnormal vaginal bleeding and mastodynia. Both these drugs are proven to have equal outcomes in reducing abdominal girth and body weight and is equally effective in their diuretic and natriuretic effect.50 mg of Eplerenone has shown better outcomes compared to 100mg of Eplerenone and spironolactone [29].

Role of Terlipressin

Terlipressin is a vasopressin analogue with high V1 receptor affinity present on vascular smooth muscle cells in splanchnic circulation leading to vasoconstriction. They act by their vasoconstrictive effects in the mesenteric artery thereby reducing the blood flow to the liver and decrease the pooling of blood in the splanchnic venous system and improve renal perfusion [30]. They partially act on the V-2 receptor present on renal collecting ducts to mobilize aquaporin channels [31]. It has a prolonged half-life of 6h and can be given through IV bolus (from 0.5–1 mg every 4–6h to 2 mg every 4h) or continuous IV infusion (from 2 mg/day to 12 mg/day) [1]. Despite other vasopressin analogues, use of terlipressin has a high priority in the treatment of HRS as it have shown improved renal function and blood flow in decompensated cirrhotic patients and similar vasoconstrictive potency with a fewer incidence of ischemic side effects compared to octapressin and ornipressin. Terlipressin can be used in HRS-1 and HRS-2. Combination of Terlipressin with albumin has shown better outcomes i.e. reversal of HRS [24]. Since terlipressin reduces the splanchnic blood pooling it can be used in renal impaired patients undergoing liver resection because of the renal protective effects and preferably after these major liver surgeries too [30].

Effect on plasma sodium

The effect of Terlipressin on V2 Receptors accounts for hyponatremia in both variceal haemorrhage and hepatorenal

syndrome. However, the frequency of hyponatremia in HRS patients will be much lower due to the saturation of V2 vasopressin receptors by complete activation of endogenous hormones in HRS [32].

The effect of albumin administration on plasma sodium has many aspects as the negatively charged albumin can exert Gibbs Donnan effect to draw the cations like sodium into the vascular Compartment as albumin shift the interstitial fluid into intravascular space thereby increasing arterial blood volume and downregulation of baroreceptor activation. This would decrease the endogenous vasopressin release as well as water retention. Many researchers have postulated that this albumin effect may take-over terlipressin induced V2 receptor activation [31].

Thus electrolyte levels and possibly neurological symptoms should be monitored frequently in patients receiving terlipressin and albumin therapy [32].

Effect of dobutamine in terlipressin therapy

Terlipressin has increased risk of serious cardiovascular events. Terlipressin constricts splanchnic blood vessels and increases mean arterial pressure which increases cardiac afterload thereby decreasing the cardiac output, cardiac reserve and heart rate. This impairment in cardiac functions can increase the mortality risk in patients with HRS, cirrhosis and ascites. Dobutamine can be used effectively compared to Noradrenaline; as it increases both cardiac output and MAP. Dobutamine is a sympathomimetic drug with high affinity to β1 and low affinity to β2 and acts by elevating cardiac output and pulse pressure without increasing the MAP and also it doesn't use the same target in resistance vessels as of terlipressin. Combination of dobutamine with terlipressin will significantly increase the heart rate, cardiac output increases plasma renin, angiotensin-II and aldosterone. Thus it is effective in reversing the cardio-suppressive effects of terlipressin. Noradrenaline can be used in an ICU setting as it can induce systemic vasoconstriction through peripheral α-2B receptors ensuing HRS reversal with acceptable safety [33, 34].

Adverse effects of Terlipressin

One of the most dangerous adverse effects of terlipressin is ischemia which has been occurred in almost 4-12 % of patients with HRS. Ischemic side effects includes ischemic skin necrosis, coronary artery ischemia, bowel necrosis, myocardial infarction. Ischemic skin necrosis is usually characterized by cyanosis of upper and lower extremities including fingers and toes [35, 36]. Management of ischemic side effects usually involves drug withdrawal, thereby leading to a high mortality rate. Most common side-effects include pallor, headache, side effects, hypertension, bradycardia [36].

Role of Vaptans

Vaptans are non-peptide vasopressin receptor antagonist with high affinity to V2 receptors in renal collecting ducts thus increasing the free water clearance contributing to their ability in mobilizing ascites and improve hyponatremia in cirrhosis patients. Even though vaptans are not associated with improved survival in cirrhotic patients, they are beneficial in dropping down the risk for hepatic encephalopathy and spontaneous bacterial peritonitis in cirrhotic patients. Certain studies have shown that use of tolvaptan for hyponatremia correction was associated with improvement in cognitive function and quality of life and 1month tolvaptan treatment accounted for positive influence in mortality risk for patients with cirrhosis with hyponatremia [37].

Role of human albumin (HA)

International guidelines recommend the use of HA for prevention of circulatory dysfunction post-paracentesis, renal failure induced by spontaneous bacterial peritonitis and diagnosis and treatment of HRS in conjunction with vasoconstrictors.[38] The key functions to homeostasis that albumin perform like anti-oxidant, ligand binding, immune-modulatory and detoxification would be impaired in patients with decompensated liver cirrhosis. Thus toxic substance like bilirubin, cytokines and endotoxins will present in high levels requiring albumin for detoxification. Albumin also binds to nitric oxide which plays a vital role in the pathophysiology of hepatorenal syndrome. Albumin also uplifts the cardiac index by exerting positive cardiac inotropic effect which counteracts oxidative stress and reduces TNF- α levels in HRS patients with refractory ascites [39].

The first-line therapy for HRS-1 is the use of terlipressin in combination with albumin. IAC guidelines recommend the use of albumin therapy should be maintained until HRS reversal or up to a maximum of 15 days with 1g/kg/day (max. 100g) of albumin for the first day followed by 20-40g/day. In terms of the cost associated with treatment, the total cost of therapy with albumin and terlipressin was less compared to albumin alone owing to reduced rates of renal impairment and decreased mortality rate contributing to more QALYs [38].

Renal replacement therapy (RRT)

Pre-liver transplant management of renal dysfunction in HRS is very essential to improve health outcomes after liver transplant (LT). If the initial treatment with albumin and terlipressin is not effective, continuous RRT should be initiated using continuous venovenous hemodialysis (CVVHD) or continuous venovenous hemodiafilteration (CVVHDF). Patients with HRS often have hyperdynamic circulation with relative hypotension, in such conditions intermittent HD is not a good option owing to its risk in the development of hypotension in those with high intracranial pressure. CVVHD is associated with improved consciousness, metabolic acidosis, hemodynamic and biochemical control contributing to cardiovascular and intracranial stability.

Indications of RRT in patients anticipating LT includes patients diagnosed with the hepatorenal syndrome with/without pulmonary edema, pneumonia, hepatic encephalopathy, uremic syndrome. Post-transplant RRT should be initiated before transplant surgery and should be continued after surgery to maintain fluid balance during LT [40, 41].

Role of cannabinoid-2-receptor activation

Tissue inflammation, oxidative stress, fibrosis formation are the driving forces in the development of renal injury in patients undergone bile duct ligation. These factors contribute to endothelial activation and inflammatory response and collapsing the renal microcirculation. In normal liver, cannabinoid 2 receptor (CB_2-R) is expressed in Kupffer cells and is associated with the activation of inflammatory cells and endothelial sinusoidal cells. Dysregulation of the endocannabinoid system

(cannabinoid receptor 1 and 2, their synthetic and metabolizing enzymes) is associated with the pathogenesis of liver cirrhosis. An experimental study on mice has shown that signaling through CB_2-R using HU-910 (a cannabinoid agonist) exerts anti-inflammatory and anti-fibrinogenic effects and may diminish the development of oxidative/ nitrative tissue injury via inhibition of TNF-α in liver and kidneys and improves renal microcirculation [45].

Transjuglar Intrahepatic Portosystemic Shunt (TIPS)

It is a rescue therapy for portal hypertension-related complications like gastric and esophageal variceal bleeding in non-responders to standard endoscopic ligation and pharmacological treatment. It is a side-to-side porto-systemic shunt obtained by connecting the intra parenchymal branch of the portal vein and hepatic vein percutaneously. This connection ensures the reduction of portal caval pressure gradient through a low resistant self-expandable metal stent. Nowadays TIPS is indicated for various complications of portal hypertension such as hepatic hydrothorax, HRS, refractory ascites, portal vein thrombosis. Due to the availability of effective pharmacological option in HRS, the use of TIPS is limited as the patients are more likely to suffer from advanced hepatic dysfunction. However, TIPS can help improve the renal function in patients awaiting liver transplant [42, 43]. The mortality rate in HRS patients undergone TIPS was significantly lower in men with no mortality benefit in women [44]. Contraindications of TIPS include congestive heart failure, severe pulmonary hypertension and pulmonary regurgitation are complete contraindications for TIPS, whereas central mass, venous thrombosis and history of hepatic encephalopathy will complicate shunt creation [43].

Non-pharmacological management of HRS

Evidence on the use of green tea extract and probiotic mixture in preventing HRS: One of the major causes of HRS is high oxidative stress and inflammation. Recent nutraceutical studies showed that dysbiosis in colonic microflora is linked with the development of chronic liver, kidney and other inflammatory diseases. Green tea is rich in flavonoids, contributing to its anti-oxidant and anti-inflammatory activity and also possesses hepato and renoprotective effects, whereas probiotics can also protect the liver by reducing the oxidative stress through its free radical scavenging activity and by inhibiting the enzyme nitric oxide synthase. An experimental study was conducted in rat models using a microencapsulated probiotic mixture (Bifidobacterium bifidum, Lactobacillus delbrueckii and Streptococcus thermophilus) with or without alcohol green tea extract for the prevention of HRS. The study revealed a significant improvement in both liver and kidney function while improving HRS with the synergistic effect of green tea extract and probiotic mixture. Also, it mentions that restoring gut micro-flora improves intestinal endotoxemia [46].

Progression and survival limitation

Thomson MJ *et al* conducted a systemic meta-analysis to determine the survival and mortality rate after HRS reversal, and concluded that outcome after type 1 HRS is poor with low survival and HRS reversal rate. Certain studies also concluded that there is a 90 day survival rate in patients who responded to terlipressin or noradrenaline therapy. A statistically significant improvement in survival was observed compared to non-responders. Thus treatment with terlipressin and albumin was associated with increase in survival rate but not in HRS reversal [47].

Studies has also concluded that use of TIPS procedure is a safe and short-term option in those with HRS and is associated with decrease in the inpatient mortality rate with non variceal bleeders [48]. Reduction in AKI stage is independent of HRS reversal, but has found to improve the overall survival in type1 HRS [49]. Reversal rate of HRS is up to 80% after liver transplant. Patients with high MELD score and low pre transplant serum sodium have good post-transplant survival in type 1 HRS [50].

Conclusion

Hepatorenal syndrome is a serious complication of decompensated liver cirrhosis with a poor prognosis. Systemic inflammation is the focal etiology behind the progression of liver cirrhosis to HRS, thus early diagnosis is essential for rapid correction of HRS and recent changes in the definition and diagnostic criteria for HRS will help identify patients at an earlier stage, improving the clinical prognosis. Identification of sensitive and reliable biomarkers would remove a major challenge in misdiagnosing acute tubular necrosis (ATN) and HRS. Treatment modalities other than liver transplant (vasoconstrictive agents and albumin therapy) may only provide short-term clinical improvement for HRS.

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