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EDITORIAL

Terlipressin and hepatorenal syndrome: What is important for nephrologists and hepatologists

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Abstract

Hepatorenal syndrome (HRS) is a reversible form of functional renal failure that occurs with advanced hepatic cirrhosis and liver failure. Despite mounting research in HRS, its etiology and medical therapy has not been resolved. HRS encompasses 2 distinct types. Type 1 is characterized by the rapid development of renal failure that occurs within 2 wk and involves a doubling of initial serum creatinine. Type 2 has a more insidious onset and is often associated with ascites. Animal studies have shown that both forms, in particular type 1 HRS, are often precipitated by bacterial infections and circulatory changes. The prognosis for HRS remains very poor. Type 1 and 2 both have an expected survival time of 2 wk and 6 mo, respectively. Progression of liver cirrhosis and the resultant portal hypertension leads to the pooling of blood in the splanchnic vascular bed. The ensuing hyperdynamic circulation causes an ineffective circulatory volume which subsequently activates neurohormonal systems. Primarily the sympathetic nervous system and the renin angiotensin system are activated, which, in the early stages of HRS, maintain adequate circulation. Both advanced cirrhosis and prolonged activation of neurohormonal mechanisms result in fatal complications. Locally produced nitric oxide may have the potential to induce a deleterious vasodilatory effect on the splanchnic circulation. Currently medical therapy is aimed at reducing splanchnic vasodilation to resolve the ineffective circulation and maintain good renal perfusion pressure. Terlipressin, a vasopressin analogue, has shown potential benefit in the treatment of HRS. It prolongs both survival time and has the ability to reverse HRS in the majority of patients. In this review we aim to focus on the pathogenesis of HRS and its treatment with terlipressin *vs* other drugs.

Key words: Heptorenal syndrome; Terlipressin; Kidney; Liver

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INTRODUCTION

Many studies have been carried out on hepatorenal syndrome (HRS); the pathophysiology and its management

however have not been completely resolved. HRS is a reversible form of functional renal failure that occurs predominantly with advanced liver disease arising from hepatic cirrhosis or severe liver injury from any condition such as severe alcoholic hepatitis or metastatic tumors[1]. The important features of HRS are characterized by peripheral vasodilation with subsequent profound intrarenal vasoconstriction, leading to decreased glomerular filtration rate (GFR)[2,3].

Currently, HRS encompasses 2 distinct types. Type 1 HRS often manifests itself rapidly; without appropriate treatment the mean survival time is approximately 2 wk[4]. The distinguishing feature of type 1 HRS is rapid progressive renal failure that occurs within 2 wk and is associated with doubling of baseline serum creatinine or a 50% reduction in creatinine clearance[5]. In more than 70% of cases there is an identifiable trigger for type 1 HRS[6-9]. A large number of studies have shown that type 1 HRS can be precipitated by preceding spontaneous bacterial peritonitis infections, gastrointestinal bleeding and large-volume abdominal paracentesis without albumin replacement[6,8]. Furthermore, type 2 HRS has a gradual onset with a steady decline in renal function. Interestingly, the hallmark for type 2 HRS is refractory ascites and often has no precipitating factors[4]. The survival time is better in type 2 HRS at approximately 6 mo[1,5]. Some would consider injudicious use of diuretics as a precipitating factor.

Importantly, the core feature of pathogenesis of HRS is peripheral arterial vasodilation, in particular in the splanchnic vasculature[10]. This develops with advanced liver cirrhosis, which causes increased resistance to blood flow with high portal pressure. In turn, to ease the pressure within the hepatic portal system, locally acting vasoactive substances are released that cause vasodilation of the splanchnic vasculature[10]. The overall resultant effect is circulatory dysfunction arising from a depleted intravascular volume that ultimately leads to poor renal perfusion and activation of compensatory mechanisms (renin angiotensin aldosterone system, sympathetic nervous system and vasopressin). These compensatory mechanisms with time become detrimental and result in sustained severe intrarenal arterial vasoconstriction with progressive physiological renal failure[2]. The pooling of blood in the splanchnic vascular bed with the associated hypoperfusion of the kidneys and the ensuing intrarenal arterial vasoconstriction forms the basis for the development of HRS.

HRS has very poor prognosis with spontaneous recovery being unlikely[2]. Treatment of HRS can be divided into medical and surgical, the latter being more beneficial. Current treatment modalities are used as a bridge to surgical intervention (liver transplant), although most patients do not survive long enough to receive a liver transplant[2]. Pharmacotherapy is the initial treatment which buys time for a liver transplant but unfortunately there is no universally agreed first-line therapy. There are a number of pharmacological agents that have been investigated in the management of HRS and thus far most drugs aim to reverse the peripheral and splanchnic vasodilation. Usually treatment is a combined therapy of vasoconstrictors with albumin to augment their efficacy[11].

Vasoconstrictive drugs such as vasopressin analogues (ornipressin, terlipressin), octreotide and noradrenaline have been used in attempts to reduce the pooling of blood in the splanchnic vasculature and the peripheral arterial vasodilation[12]. A few studies have investigated ornipressin combined with albumin or dopamine and they have been shown to reverse HRS[13-15]. Globally the use of ornipressin has been abandoned in HRS because of the high risk of an adverse event, in particular ischemic events. Other studies have shown that with the use of potent vasoconstrictors such as ornipressin, the result can be ischemic mesenteric mucosa, myocardial ischemia, and associated ventricular arrhythmias[16]. A safe alternative treatment is terlipressin (vasopressin analogue) which so far has shown promising results.

Several studies have confirmed that terlipressin combined with albumin achieves acceptable GFR and it almost normalizes the plasma creatinine levels in 42% to 77% of cases[17-20]. The aim of the current review is to evaluate the recent developments made in the pathogenesis of HRS and the role of terlipressin, including its possible mechanism of it action.

PATHOGENSIS OF HRS

The etiopathogenesis of HRS has not been fully resolved and there are possible theories to explain it at a cellular and molecular level. The defining feature of HRS is profound vasoconstriction of the renal vasculature due to inadequate blood flow to the kidneys[21-24]. The culmination of several factors leads to the development of HRS: (1) portal hypertension (PHT); (2) altered peripheral blood circulation; (3) activation of the sympathetic nervous system; and (4) the release of chemical mediators.

PHT AND NITRIC OXIDE

Over time, liver cirrhosis leads to structural changes at both a microscopic and macroscopic level within the hepatocytes. The pressure within the hepatic microcirculation becomes raised and the so-called sinusoidal PHT occurs[25]. Furthermore, this is complemented by the ongoing changes taking place within the myofibroblasts, stellate cells and portal venules which all contribute towards the development of increased resistance to portal blood flow[26,27]. Most research on animals has suggested 2 possible theories to explain the development of PHT: (1) "forward theory" - this theory puts forward that PHT arises as a direct consequence of increased resistance to portal inflow; and (2) "backward theory" which proposes that PHT occurs due to high portal blood inflow because of a hyperdynamic circulation[28,29]. Furthermore, it is insinuated that this abnormally high portal blood inflow sustains the PHT[30].

In spite of the etiology of PHT, some of the portal venous blood gets redirected *via* collaterals vessels and this is partially to take pressure off the portal system[31]. Gradu-

ally, with persistent PHT, local and systemic changes occur; neurohormonal systems are activated and locally produced vasoactive substances such as nitric oxide are released[32]. Other locally acting vasodilatory substances released include carbon monoxide and prostacyclin[33]. Nitric oxide however is widely believed to be one of the main culprits for initiating the splanchnic arterial vasodilation[34].

In animal models nitric oxide has been shown to play an important role in vascular tone and splanchnic vasodilation[35,36]. In other animal studies, it is postulated that the production of nitric oxide may be related to bacteria stimulating macrophages which in turn induce nitric oxide synthase (NOS)[37-39]. NOS is an enzyme that forms nitric oxide from L-arginine, which is found throughout the body in numerous different types of cells. In addition, NOS has been shown to have 3 isoforms which are NOS I - neuronal NOS (nNOS), NOS Ⅱ - inducible NOS (iNOS) and NOS Ⅲ - endothelial NOS (eNOS)[40-42].

Isoform nNOS is primarily found in the central nervous system and it has been shown to have a key role in controlling blood pressure. Several studies on rats have demonstrated that by inhibiting this isoenzyme it generates increased sympathetic activity with ensuing tachycardia, and hypertension[43-45]. Conversely, iNOS is present in humans in several tissues including hepatocytes and alveolar macrophages; its release is induced by several cytokines including interleukin 1, interferon γ, tumor necrosis factor and lipopolysaccharides[46,47]. Finally eNOS, as the name suggests, is predominantly found in endothelial cells in humans in both arterial and venous vessels[48,49]. In the literature, eNOS has been shown to be involved in the peripheral arterial vasodilation that occurs in HRS and there are raised levels of eNOS in the circulation[48]. Overall eNOS has an important role in maintaining sympathetic vascular tone and can be synthesized within the endothelium in response to stimuli.

HYPERKINETIC CIRCULATION AND COMPENSATORY MECHANISM

The hemodynamic changes that develop in cirrhosis in the splanchnic circulation have been studied extensively, and only slow progress has been made in determining its pathophysiology. A number of plausible theories have been postulated in the last 2 decades based on both *in vitro* and *in vivo* studies. Hyperdyanamic circulation is a phenomena that happens over a period of time as a direct consequence of long standing PHT (Figure 1)[50]. The hallmarks of this circulatory dysfunction are tachycardia, increased cardiac output and abnormally low peripheral vascular resistance with decreased arterial blood pressure[31].

Hyperkinetic circulation develops in several steps: (1) splanchnic and peripheral vasodilation; (2) an increase in total blood volume with inadequate circulating volume; (3) increased cardiac output; and (4) the activation of a compensatory mechanism. Initially there is pooling of blood in the splanchnic vasculature due to PHT and this causes decreased circulatory volume.

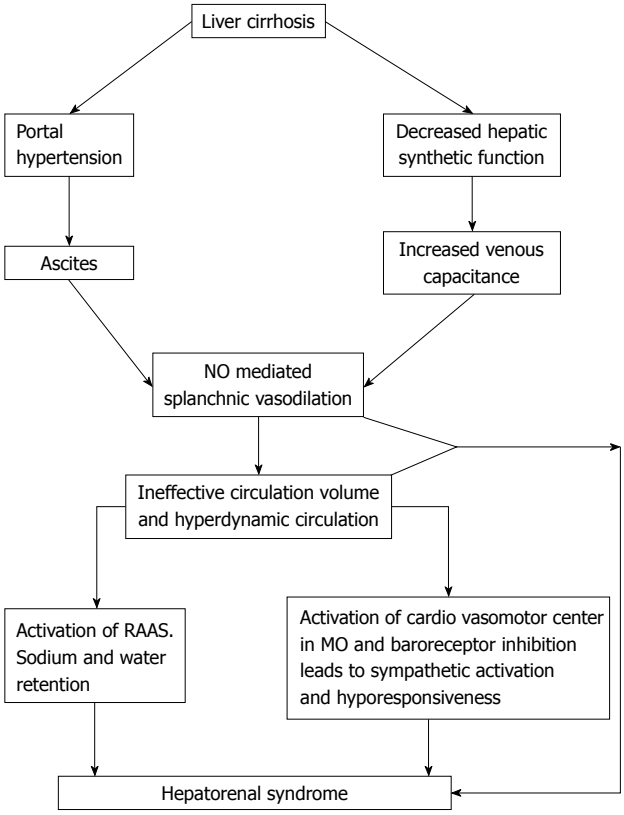

Figure 1 Flow chart showing the vicious cycle that develops with decompensated liver cirrhosis and the serious of events that lead to hepatorenal syndrome. NO: Nitric oxide; RAAS: Renin angiotensinogen aldosterone system; MO: Medulla oblongata.

One of the earliest indicators of a hyperdynamic circulation is the redistribution of blood volume into the splanchnic circulation. This event has been demonstrated in Doppler ultrasonography studies in which patients with cirrhosis had remarkably high splanchnic blood flow when compared to normal subjects[51]. The development of increased blood flow to splanchnic circulation and the pooling of blood produce a decreased circulating volume that triggers neurohormonal responses.

SYMPATHETIC NERVOUS SYSTEM, CARDIAC OUTPUT AND THE BARORECEPTORS REFLEX

A low circulating volume (low blood pressure) is detected by the baroreceptors or pressoreceptors located mainly in the internal carotid artery (carotid sinus) and ascending aorta. They are also found in small quantities in the wall of almost every large artery in the neck and thorax[1]. These are pressure sensitive receptors which are physiologically inactivated when the aforementioned arteries become less stretched as a result of low blood pressure (Figure 1)[52]. Consequently, the carotid and aortic baroreceptors signal conduction to the cardio and vasomotor regulatory centers in the medulla oblongata, *via* the glossopharyngeal and vagus nerves, respectively, is subdued. Thus, the cardio-

vasomotor regulatory centers become more active and sequentially induce the sympathetic nervous system to become active while suppressing parasympathetic (vagus nerve) stimulation to the heart. The sympathetic nervous system through the cardiac accelerator nerve increases the heart rate and cardiac output. Furthermore, the adrenal medulla, under the influence of the sympathetic nervous system, releases both adrenaline and noradrenaline. This eventually leads to an increase in mean arterial pressure through increased cardiac output and peripheral vascular resistance by acting on adrenergic receptors. The sympathetic response is further augmented by the activation of the RAAS and the release of vasopressin[53]. Unfortunately, those complex neurohormonal compensatory responses to low blood pressure are temporary and the whole system that comprises the baroreceptors, RAAS and vasopressin becomes adapted and mal-responsive to the low circulating volume stimulus within 48-72 h[4]. Consequently all the above outlined responses are reversed resulting in profound hypotension, renal hypoperfusion and worsening renal failure.

RENIN ANGIOTENSIN ALDOSTERONE SYSTEM

Arterial hypotension and reduced blood flow to the kidney results in decreased sodium delivery to the macula densa which in turn causes the release of renin from the juxtaglomerular apparatus[54]. The renin release is the rate determining step for the activation of the RAAS. The activation of RAAS causes sodium and water reabsorption and vasoconstriction of the renal arteries (Figure 1)[55]. These compensatory mechanisms maintain effective circulation in the early stages of the disease (compensated) but with time their effects eventually become deleterious and lead to the development of complications. These include ascites, hyperkinetic circulation, nitric oxide release, renal failure, and increased venous capacitance with decreased venous compliance. Essentially all these culminate to form the bases of HRS[55].

Liver cirrhosis has been shown to be associated with activation of RAAS but also an increase in vasopressin secretion[56]. The activation of RAAS may contribute to decreased renal perfusion[56]. Importantly, albumin administration has been shown to be associated with a decrease in plasma renin level[57]. In contrast, administration of vasopressin does not substantially change renal perfusion, though it induces splanchnic vasoconstriction[57]. This may explain the potential benefit of administration of vasopressin and its analogues in HRS. The progression of PHT is associated with an increase in vasodilation of the splanchnic circulation and marked resistant to vasopressin. It is likely that further research is needed to address the interaction between RAAS and vasopressin.

In addition, the activation of the RAAS has an important role in hemodynamic regulation in the liver as well as proliferation of vascular smooth muscle cells and fibrosis through 2 well coordinated complementary pathways: (1) vasoconstriction/proliferative pathway, incorporating the angiotensin converting enzyme (ACE), angiotensin (Ang) Ⅱ-Ang Ⅱ type 1 (AT1) receptor; and (2) a counter- regulatory vasodilatation/antiproliferative pathway, involving ACE2-Ang-(1-7)-Mas receptor[58]. It is important to point out that the ACE, vasoconstriction/proliferation pathway induces contraction and proliferation of hepatic stellate cells, which lead to fibrosis[58]. In contrast, activation of ACE2-Ang-(1-7) is not only associated with liver cirrhosis-induced splanchnic and systemic vasodilatation but also anti-fibrotic effects[58].

Vilas-Boas *et al*[59] suggested that the administration of a combination of propranolol and ACE inhibitor or AT1 receptor blocker may have potential benefit in cirrhotic patients. Furthermore, administration of propranolol *per se* has been shown to be associated with unfavorable consequences on the 2 main RAAS components, Ang Ⅱ and Ang(1-7), in the splanchnic and peripheral circulation[59]. In contrast, inhibition of RAAS by ACE inhibitors and AT1 receptor blockers has been shown to be associated with potential benefit in slowing progression of liver fibrosis and even cardiac and renal fibrosis[60].

Interestingly, it has been hypothesized that the effect of Ang Ⅱ dominates in advanced liver disease while the effect of Ang(1-7) dominates in moderate liver disease[61]. Therefore, the RAAS can be viewed as a dual system that leads to vasoconstriction, fibrosis, vasodilatation and antifibrosis. However, further research is urgently needed to establish a therapeutic benefit of the dual function of the RAAS in targeting liver disease and preventing fibrosis in humans and, in particular, in the management of HRS.

DETRIMENTAL EFFECTS OF THE SYMPATHETIC NERVOUS SYSTEM AND RAAS

These wonderful compensatory mechanisms with prolonged activation result in even more increased sodium and water retention with a subsequent increase in total circulatory volume. RAAS, with its overall effect of salt and fluid retention contributes to the development of ascites usually in the presence of PHT. In addition, splanchnic vasodilation appears to be one of main culprits in the formation of ascites[50]. Ascites develops when there is increased sinusoidal pressure which forces fluid to leak into the abdominal cavity[1]. Ascites further fuels the constant activation of the RAAS and the sympathetic nervous system which fail to maintain effective circulating volume.

The lack of response to neurohormonal mechanisms in the latter stages of cirrhosis may be due to several factors: (1) nitric oxide-mediated pooling of blood in splanchnic vascular bed; (2) hyporesponsiveness of splanchnic vasodilation to neurohormonal mechanism; (3) ascites; and (4) downregulation of receptors.

Eventually the pooled blood in the splanchnic circulation cannot be utilized fully in the presence of ineffective

circulation. This is on account of the fact that the reservoir of blood in the splanchnic circulation continues to increase and is mediated by locally-produced nitric oxide. A recent study by Li *et al*[62] demonstrated that nitric oxide caused changes in mesenteric venous capacitance and increased pooling of blood in rats with liver cirrhosis. In this study it was shown that the cirrhotic rats had a nitric oxide-mediated increase in venous capacitance and decrease in compliance. Nitric oxide is produced locally by eNOS which is activated by the high shear stress in the splanchnic vascular endothelium, which is caused by the increased splanchnic blood flow. In both animal and human studies, nitric oxide appears to be the main orchestrator of the splanchnic vasodilation that facilitates the pooling of blood[63,64], *via* its direct action on the vascular smooth muscles.

Additionally, it is widely accepted that nitric oxide antagonizes the sympathetic and RAAS-driven vasoconstriction thus inducing vasodilatation of the splanchnic vascular bed. Accordingly, ineffective circulation continues to trigger neurohormonal responses, though in the latter stages of the disease there is hyporesponsiveness to these compensatory mechanisms. In the early stages of compensated liver cirrhosis, the neurohormonal activation is able to overcome the splanchnic vasodilation and maintain an acceptable circulating volume. However with decompensated liver cirrhosis; and increased PHT, the hyporesponsiveness is often an indicator of progression towards the end stage.

It is suggested that the hyporesponsiveness may be due to desensitization and downregulation of adrenergic receptors. In cirrhotic rats there appears to be β-adrenergic receptor hyporesponsiveness to catecholamines[65]. This concept is not new; previous studies looking at heart failure have shown that prolonged activation of the neurohormonal response leads to a downregulation of β-adrenergic receptors[66]. The hyporesponsiveness of the myocardium to catecholamine stimulation that is seen in cirrhosis is termed cirrhotic cardiomyopathy[67].

FUNCTIONAL RENAL FAILURE

The renal system, through autoregulation, maintains a physiologically acceptable GFR over a range of blood pressures. Autoregulation consists of myogenic and neurohormonal responses. The development of a hyperkinetic circulation results in renal hypoperfusion despite increased total circulating volume. Initially with low blood pressure, the kidneys respond with smooth muscle contraction in the vessels (myogenic response), which helps to maintain the perfusion pressure[1]. This response alone is not adequate, therefore the sympathetic nervous system and RAAS are activated and subsequently lead to renal vasoconstriction. The peripheral vasodilatation that occurs is perceived by the kidneys as a hypovolemia, that continues to promote renal vasoconstriction. The resultant effect is reduced GFR, oligo-anuria, raised plasma creatinine and the development of hepatorenal failure[2].

Renal biopsies in HRS patients have shown remarkably normal renal histology architecture despite the dismal renal function. The findings have led to the term "reversible functional renal failure" being coined[22]. The primary problem causing renal failure is liver cirrhosis and this functional renal failure can be reversed with liver transplantation. Kidney transplants from palliated patients with HRS into those with intrinsic renal failure, have remarkably been show to have reversed to normal renal function[68,69]. This further supports the concept of reversibility of functional renal failure in patients with HRS. The definitive treatment for HRS is liver transplantation; however with increasing shortages of organ donation and with long waiting lists, patients are more often than not succumbing to the dismal prognosis of HRS. Nevertheless treatment with vasopressin analogues, in particular terlipressin, has been shown to reverse the renal failure and can be used as a bridge to definitive treatment (liver transplant).

TERLIPRESSIN AS POTENTIAL TREATMENT FOR HRS

Terlipressin, an analogue of vasopressin, is used as potential treatment of HRS. In this review we focus on clinical trials and their strengths and weaknesses. It is worth mentioning that in the majority of these studies, terlipressin was used in combination with albumin. Furthermore, other trials compared the effect of terlipressin with noradrenaline. We included clinical trials with evidence-based medicine. Hence, the subsequent discussion will focus on the impact of terlipressin *vs* placebo and terlipressin *vs* noradrenaline with and without albumin.

Terlipressin and clinical trials

Terlipressin (without albumin) *vs* placebo: Hadengue *et al*[70] carried out a double-blind, crossover, randomized study in 9 patients with type 1 HRS. The patients received terlipressin (2 mg/d for 2 d) and a placebo for 2 d in a randomized order. Terlipressin administration significantly increased creatinine clearance and urine output, but did not significantly change urinary sodium concentration. Urinary sodium excretion was not significantly different after placebo administration or terlipressin administration. Terlipressin administration significantly decreased plasma concentrations of renin and aldosterone but not atrial natriuretic peptide levels, and these biochemical changes were not seen in the placebo group. The study by Solanki *et al*[19] was a randomized, controlled, single-blind trial. They assigned 24 consecutive patients with HRS to treatment with terlipressin 1 mg iv at 12 h intervals (group A, $n = 12$) or placebo at 12 h intervals (group B, $n = 12$). The end-point of the study was improvement in renal function defined as reversal of HRS and survival at 15 d. Terlipressin administration was shown to be associated with an improvement in parameters of renal function, mean arterial blood pressure and importantly reversal of HRS in 5 of the 12 patients in group A.

Table 1 Summary of effect of terlipressin associated with albumin on hepatorenal syndrome

Study	Main outcome
Sanyal *et al*[72], 2008	Terlipressin administration with albumin shown to be associated with improvement in renal function and appeared superior to placebo in reversing type 1 HRS
Martín-Llahí *et al*[73], 2008	Terlipressin administration with albumin shown to be associated with improvement in renal function in patient with liver cirrhosis and type 1 HRS, without significant impact on 3-mo survival
Neri *et al*[74], 2008	Terlipressin administration with albumin shown to be associated with improvement in renal function in patients with type 1 HRS and also a high probability of survival
Uriz *et al*[17], 2000	Terlipressin associated with albumin appeared to be a safe and effective treatment of HRS and decreased the frequent ischemic complications associated with terlipressin treatment alone. Terlipressin associated with albumin therapy was associated with marked improvement in renal function, reversal of HRS and improvement in circulatory function with an increase in mean arterial blood pressure

HRS: Hepatorenal syndrome.

Interestingly, Testro *et al*[71] reviewed outcomes of 69 patients treated with terlipressin between 2001 and 2005. Their findings showed that 49 episodes (71%) of HRS were type 1, and 20 episodes (29%) were type 2. Forty-one (59.4%) patients responded to terlipressin. Twenty-one (30.4%) patients survived; 17 (81%) had type 1 HRS while 4 (19%) had type 2 HRS ($P = 0.27$). The only factor predicting transplant-free survival was type 1 HRS. No patients with type 2 HRS survived without transplantation ($P = 0.02$). These trials clearly showed the potential benefit of administration of terlipressin in individuals with HRS. However, Terlipressin administration was associated with minimal reversible ischemic events e.g. crampy abdominal pain and cardiac arrhythmias. We suggest that randomized clinical trials are now warranted.

Terlipressin (with albumin) *vs* placebo: Interestingly, concomitant administration of terlipressin and albumin is shown to be associated with better clinical outcomes. A summary of studies that used terlipressin (with albumin) *vs* placebo is provided in Table 1.

Terlipressin *vs* noradrenaline: The use of noradrenaline, a cheap and widely available drug, in the management of HRS was shown to be as effective as terlipressin but associated with increased risk of ischemic events. Data from an unblinded, pilot study suggested that noradrenaline was as effective and safe as terlipressin in patients with HRS. Twenty-two consecutive cirrhotic patients with HRS (9 with type 1 HRS; 13 with type 2 HRS) were randomly assigned to treatment with noradrenaline (0.1-0.7 μg/kg per minute) and albumin (10 patients) or with terlipressin (1-2 mg/4 h) and albumin (12 patients). Treatment was administered until HRS reversal or for a maximum of 2 wk. Reversal of HRS was observed in 7 of the 10 patients (70%) treated with noradrenaline and in 10 of the 12 patients (83%) treated with terlipressin. Treatment led, in both groups, to a significant improvement in renal and circulatory function; no patient developed signs of myocardial ischemia[75]. Sharma *et al*[76] reported similar beneficial results in treating HRS with noradrenaline, however, they also reported that 2 patients had ventricular ectopies with noradrenaline. We suggest that further studies are urgently needed to evaluate the use of noradrenaline as potential treatment for HRS.

Terlipressin and meta-analyses

Several meta-analyses have been conducted to determine the effect of terlipressin in HRS with regard to the duration of treatment, infusion of albumin and comparison with noradrenaline. Dobre *et al*[77] concluded in their meta-analysis that terlipressin administration was associated with improvement in HRS reversal and that noradrenaline has the same effect as terlipressin in improving surrogate markers of HRS. Sagi *et al*[11] showed that the risk ratio for reversal in type 1 HRS with terlipressin therapy was 3.66 [95% confidence interval (CI): 2.15-6.23]. Recurrence of HRS was low (8%). Serious side effects requiring discontinuation of therapy were seen only in 6.8% of patients on terlipressin therapy. There was a trend towards improved transplant-free survival at 90 d in the Terlipressin group (relative risk 1.86, 95% CI: 1.0-3.4, $P = 0.05$). The conclusion of their meta-analysis was that terlipressin is effective in reversing HRS type 1 and recurrence of HRS is rare with at least 14 d of therapy and associated with an increased survival. Importantly, Fabrizi *et al*[78] showed in their meta-analysis that discontinuation of terlipressin therapy was associated with a significant increase in the number of relapses. Furthermore, Fabrizi *et al*[79], in another meta-analysis, showed that terlipressin was more effective in reversing HRS than placebo without apparent impact of terlipressin on survival in HRS patients. This may again suggest the need for large clinical trials addressing the impact of terlipressin in HRS patient survival. Interestingly, administration of albumin with terlipressin showed a reduction in mortality in type 1 HRS[10]. Therefore, the current evidence suggests that terlipressin can have a potential benefit in treating HRS and that an improvement in survival can be achieved with its concomitant administration with albumin.

CONCLUSION

HRS continues to be a challenging task to manage following chronic liver cirrhosis. The grave prognosis and the short survival times have fuelled great interest in clinical

trials; its reversibility creates scope for prolonging both survival and quality of life. The current literature reviewed has further re-enforced terlipressin as a potential first-line treatment in HRS**.** Terlipressin has so far shown to increase survival rates and reverse functional renal failure. The increased neurohormonal response, especially of the RAAS, has been decreased with the administration of terlipressin. This subsequently improves circulatory dysfunction and lowers plasma creatinine levels near to baseline values. The effects of nitric oxide, which is a factor in the deleterious neurohormonal response, appears to be overcome by the administration of terlipressin through unknown mechanisms.

In addition, terlipressin has few adverse side effects, which allows patients to continue with treatment in order to achieve desirable effects. At present however, we acknowledge that there are a limited number of randomized, controlled studies carried out on terlipressin and therefore there is a real need for large multi-centered trials to be carried out. We recommend that terlipressin, with concomitant administration of albumin, may be the first line treatment in the management of HRS.

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