Practice guidance for the use of terlipressin for liver cirrhosis–related complications

Ther Adv Gastroenterol

2022, Vol. 15: 1–19

DOI: 10.1177/17562848221098253

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Abstract

Background: Liver cirrhosis is a major global health burden worldwide due to its high risk of morbidity and mortality. Role of terlipressin for the management of liver cirrhosis–related complications has been recognized during recent years. This article aims to develop evidence-based clinical practice guidance on the use of terlipressin for liver cirrhosis–related complications.

Methods: Hepatobiliary Study Group of the Chinese Society of Gastroenterology of the Chinese Medical Association and Hepatology Committee of the Chinese Research Hospital Association have invited gastroenterologists, hepatologists, infectious disease specialists, surgeons, and clinical pharmacists to formulate the clinical practice guidance based on comprehensive literature review and experts' clinical experiences.

Results: Overall, 10 major guidance statements regarding efficacy and safety of terlipressin in liver cirrhosis were proposed. Terlipressin can be beneficial for the management of cirrhotic patients with acute variceal bleeding and hepatorenal syndrome (HRS). However, the evidence regarding the use of terlipressin in cirrhotic patients with ascites, post-paracentesis circulatory dysfunction, and bacterial infections and in those undergoing hepatic resection and liver transplantation remains insufficient. Terlipressin-related adverse events, mainly including gastrointestinal symptoms, electrolyte disturbance, and cardiovascular and respiratory adverse events, should be closely monitored.

Conclusion: The current clinical practice guidance supports the use of terlipressin for gastroesophageal variceal bleeding and HRS in liver cirrhosis. High-quality studies are needed to further clarify its potential effects in other liver cirrhosis–related complications.

Keywords: complications, liver cirrhosis, management, practice guidance, terlipressin

Received: 11 March 2022; revised manuscript accepted: 12 April 2022.

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Introduction

Liver cirrhosis is the 11th most common cause of death and, together with liver cancer, accounts for 3.5% of all deaths worldwide.[1] It imposes a substantial health burden on many countries. There were 10.6 million cases of decompensated cirrhosis and 112 million cases of compensated cirrhosis globally in 2017.[2] Ascites, gastroesophageal variceal bleeding, hepatic encephalopathy, and hepatorenal syndrome (HRS) are common complications of liver cirrhosis,[3–5] which are mainly secondary to increased portal pressure,[6,7] hyperdynamic circulatory state,[8–11] and systemic inflammation.[12] Terlipressin is widely used for

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Table 1. Key guidance statements regarding the terlipressin in patients with liver cirrhosis.

Gastroesophageal variceal bleeding
Guidance Statement 1. Terlipressin is recommended for the treatment of gastroesophageal variceal bleeding in liver cirrhosis.
Guidance Statement 2. Terlipressin should be considered for the management of acute gastrointestinal bleeding in patients with liver cirrhosis before endoscopy, if gastroesophageal variceal rupture is suspected as the major source of bleeding.
Guidance Statement 3. Terlipressin may be preferred in cirrhotic patients with acute gastrointestinal bleeding and renal dysfunction.
Hepatorenal syndrome
Guidance Statement 4. Terlipressin is recommended for the treatment of type-1 hepatorenal syndrome in liver cirrhosis.
Ascites
Guidance Statement 5. Terlipressin should be considered for severe or refractory ascites in cirrhotic patients, if diuretics are ineffective or patients cannot tolerate diuretic-related adverse reactions.
Post-paracentesis circulatory dysfunction
Guidance Statement 6. Terlipressin could be considered for the prevention of post-paracentesis circulatory dysfunction in cirrhotic patients with ascites undergoing large volume paracentesis (>5 L).
Bacterial infections
Guidance Statement 7. Terlipressin should be considered in cirrhotic patients with bacterial infections to improve systemic hemodynamic status, microcirculation, and organ perfusion.
Hepatic resection
Guidance Statement 8. Terlipressin can decrease intraoperative portal pressure, blood loss, and amount of blood transfused and postoperative portal pressure in cirrhotic patients undergoing hepatic resection.
Liver transplantation
Guidance Statement 9. Terlipressin is considered for the improvement of systemic hemodynamic status and renal function in cirrhotic patients undergoing liver transplantation.
Terlipressin-related adverse events
Guidance Statement 10. Terlipressin-related adverse events mainly include gastrointestinal symptoms, electrolyte disturbance, and cardiovascular and respiratory adverse events. They can be often resolved by dosage reduction or drug withdrawal and symptomatic treatment.

the management of gastroesophageal variceal bleeding and HRS. However, its optimal dosage and duration, timing of drug withdrawal, and monitoring and management of adverse events remain controversial.

Methods

Hepatobiliary Study Group of the Chinese Society of Gastroenterology of the Chinese Medical Association and Hepatology Committee of the Chinese Research Hospital Association have selected a working group of experts in charge of organizing the online conferences and of writing this document. Four leaders/co-leaders of this working group defined the methodology used and 10 major topics involved for the practice guidance (Table 1). The members of this working group were selected based on their role, clinical experiences, and researches in the field of management of liver cirrhosis and mainly included gastroenterologists, hepatologists, infectious disease specialists, surgeons, and clinical pharmacists. Four major members were responsible for briefly presenting

the background for each of the 10 major topics, searching the literature in the PubMed database by using search items 'Cirrhosis' AND 'Terlipressin', systematically reviewing the current evidence and then elaborating the provisional statements for the practice guidance. Since March 2021, these provisional statements were circulated by sending emails among the members of this working group. Thus, each member can independently carry out a systematic literature search, using the PubMed database, to assess the validity of these statements. The four major members gave point-to-point responses to their comments and made corresponding revisions after their discussions. Notably, a guidance document is different from a guideline. Guidelines are developed by a multidisciplinary panel of experts who rate the quality (level) of the evidence and the strength of each recommendation using the Grading of Recommendations Assessment, Development, and Evaluation system. A guidance document is developed by a panel of experts in the topic, and guidance statements, not recommendations, are put forward to help clinicians understand and implement the most recent evidence. On 7 September 2021, an online conference was held and recorded, and the revised statements were discussed among all members of this working group. All relevant comments were considered to further improve the quality of the statements. Subsequently, the updated version of practice guidance was sent for final corrections, comments, and approval of the practice guidance recommendations. Following a Delphi process,[13] all members of this working group were asked to specify whether they approved each recommendation and, if not, to justify their disagreement. Corrections and comments were considered in the final version of the practice guidance. It should be acknowledged that these statements will be further updated after more clinical practice experiences and high-quality evidence are accumulated in future. All members of the working group were also asked to declare any potential conflict of interests. The present work followed the AGREE Reporting Checklist.[14]

Mechanisms of vasopressin and its analogues

Vasopressin and its analogues exert pharmacological effects by binding to V receptors, mainly including V_1 and V_2 receptors. V_1 receptors are primarily distributed on the surface of vascular and uterine smooth muscle cells, and activated V_1 receptors can constrict vascular smooth muscle and increase vascular resistance, thereby reducing splanchnic blood flow and increasing effective circulating blood volume, cardiac output, and blood pressure.[15,16] V_2 receptors are located at the basolateral membrane of collecting ducts, and activated V_2 receptors can promote the synthesis of aquaporin, then insert into the apical membrane of renal collecting duct and endothelial cells, thereby increasing water reabsorption from the renal collecting duct.[15]

Vasopressin and its analogues include pituitrin, arginine vasopressin (antidiuretic hormone), desmopressin, and glycine vasopressin (terlipressin). Pituitrin and terlipressin have strong affinity for V_1 receptors and are commonly used for visceral hemostasis.[17,18] Antidiuretic hormone and desmopressin have strong selectivity for V_2 receptors and are commonly used for the treatment of central diabetes insipidus.[19] At present, pituitrin has been rarely used for the treatment of liver cirrhosis–related complications due to its higher incidence of adverse events.[20,21]

Terlipressin is a synthetic analogue of vasopressin, in which lysine replaces arginine at the eighth position of vasopressin peptide chain, and an amino acid branch chain composing of three glycines at cysteine is added. Its molecular formula is $C_{52}H_{74}N_{16}O_{15}S_2$, relative molecular mass is 1227.37, and plasma half-life is 24 ± 2 min. Terlipressin is degraded by protease into active product lysine-vasopressin. Its affinity for V_1 receptors is 6-fold higher than that for V_2 receptors,[22] which can have a stronger effect on splanchnic vasoconstriction, thereby reducing portal pressure and increasing renal perfusion.[23]

Use of terlipressin in liver cirrhosis–related complications

Gastroesophageal variceal bleeding in liver cirrhosis

Guidance Statement 1. Terlipressin is recommended for the treatment of gastroesophageal variceal bleeding in liver cirrhosis.

Acute gastrointestinal bleeding is one of serious complications of liver cirrhosis, and gastroesophageal varices are the most common source of gastrointestinal bleeding in liver cirrhosis.[24] Terlipressin has been recommended as the first-line treatment of gastroesophageal variceal bleeding.[25–27] In 1990, a randomized controlled trial

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(RCT) for the first time explored the role of terlipressin for the treatment of acute esophageal variceal bleeding in cirrhotic patients.[28] Sixty patients were assigned to terlipressin ($n=29$) and placebo ($n=31$) groups. The rate of control bleeding was significantly higher in patients receiving terlipressin than those receiving placebo (90% *versus* 59%, $p<0.01$). Since then, several studies have also confirmed the efficacy of terlipressin in cirrhotic patients with acute variceal bleeding.[27,29,30] Recently, a meta-analysis of 30 RCTs with 3344 cases compared the efficacy and safety of terlipressin *versus* placebo, pituitrin, somatostatin, octreotide, endoscopic therapy, or balloon tamponade for the management of acute variceal bleeding in cirrhotic patients.[31] Patients receiving terlipressin had a significantly higher rate of control bleeding and a lower mortality than those receiving placebo, but were not significantly different from those receiving pituitrin, somatostatin, or octreotide. The incidence of adverse events was significantly lower in patients receiving terlipressin than those receiving pituitrin [odds ratio (OR) R= 0.15, $p=0.02$], but higher than those receiving somatostatin (OR = 2.44, $p=0.04$). Terlipressin alone had significantly higher 5-day treatment failure than endoscopic variceal ligation plus terlipressin (OR = 14.46, $p=0.01$). Terlipressin group had a significantly lower 30-day mortality than balloon tamponade group (OR = 0.05, $p<0.01$).[31] In addition, terlipressin in combination with octreotide or somatostatin did not further reduce portal pressure.[32,33] The European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD) guidelines recommend that the dosage of terlipressin is 2 mg/4 h by intravenous boluses for 2–5 days.[27,29,30] Notably, recent evidence suggested that continuous infusion of terlipressin could reduce portal pressure stably and increase treatment success rate.[34,35] Considering the use of terlipressin in our clinical practice,[36] we recommend that the initial dosage of terlipressin is 1–2 mg/4 h by slowly intravenous boluses (>1 min) or continuously intravenous infusion and that the maintenance dosage is 1–2 mg/6 h by continuously intravenous infusion. Generally, the maximum daily dosage is 120–150 μg/kg, and its duration is 3–5 days. Certainly, the dosage and duration of terlipressin can be adjusted according to the severity of variceal bleeding and patients' conditions.

Guidance Statement 2. Terlipressin should be considered for the management of acute gastrointestinal bleeding in patients with liver cirrhosis before endoscopy, if gastroesophageal variceal rupture is suspected as the major source of bleeding.

Non-variceal gastrointestinal bleeding in cirrhotic patients is mainly secondary to peptic ulcer and gastric and duodenal mucosal erosion, and so on.[37] Endoscopy is the golden diagnostic approach for the source of gastrointestinal bleeding.[38] However, in real-world clinical practice, not all patients with acute gastrointestinal bleeding can undergo emergency endoscopy, especially in primary hospitals lacking endoscopy equipment and experienced endoscopists. Real-world studies also showed that 60–80% of patients with acute gastrointestinal bleeding could undergo endoscopy.[39,40] Accordingly, the source of gastrointestinal bleeding was unclear in about 20% of patients. The first-line treatment for acute non-variceal gastrointestinal bleeding is high-dose proton pump inhibitors,[41–43] but clinicians also immediately prescribe vasoactive drugs when the source of acute gastrointestinal bleeding is unknown in cirrhotic patients and then adjust their treatment strategy after endoscopy.[27,44] This is primarily because the source of gastrointestinal bleeding is variceal in a majority of cirrhotic patients.[45,46] In fact, in several well-designed clinical trials, vasoactive drugs were given before endoscopy in cirrhotic patients with acute gastrointestinal bleeding.[47–49] Taken together, terlipressin can be considered for the management of acute gastrointestinal bleeding when the source of bleeding is unknown or before endoscopy.

Guidance Statement 3. Terlipressin may be preferred in cirrhotic patients with acute gastrointestinal bleeding and renal dysfunction.

Renal dysfunction is a common complication of acute gastrointestinal bleeding in liver cirrhosis with an incidence of 16–25%.[50,51] It can significantly increase the risk of death in such patients with a short-term mortality of 37–55%.[51–53] A pilot study demonstrated that terlipressin could associate with a significant decrease of serum cystatin-C concentration.[54] By comparison, early studies found that octreotide and somatostatin could not improve renal function.[55–57] Recently, a multicenter retrospective study showed that terlipressin could significantly decrease the in-hospital mortality as compared to octreotide/somatostatin (3.6% *versus* 20.0%, $p=0.04$) in cirrhotic patients with acute gastrointestinal bleeding and renal dysfunction

defined as serum creatinine concentration of >133 mmol/L.[58] Similarly, another retrospective study also suggested that terlipressin could decrease the 30-day mortality as compared to somatostatin (42.3% *versus* 52.6%) in cirrhotic patients with esophageal variceal bleeding and renal dysfunction, but the difference was not statistically significant (hazard ratio = 1.49, $p = 0.09$).[59] Collectively, terlipressin may be a preferred choice of treatment in cirrhotic patients with acute gastrointestinal bleeding and renal dysfunction.

Hepatorenal syndrome in liver cirrhosis

Guidance Statement 4. Terlipressin is recommended for the treatment of type-1 hepatorenal syndrome in liver cirrhosis.

HRS, a functional renal failure, is related to a reduction of effective arterial blood volume and mean arterial pressure (MAP) caused by visceral vasodilation in liver cirrhosis, which can activate sympathetic nervous and renin–angiotensin–aldosterone systems. In addition, it is associated with increased synthesis of vasoactive mediators, such as cysteinyl leukotrienes, thromboxane-A2, F2-isoprostane, and endothelin-1, which affects renal blood flow or glomerular microcirculation.[60] Traditionally, HRS is classified into type 1 and type 2. Type 1 HRS is characterized by rapidly progressive renal failure with doubling of the initial serum creatinine concentration to a level greater than 226 mmol/L (i.e. 2.5 mg/dl) within 2 weeks. Type 2 HRS is characterized by steady or slowly progressive renal failure with a change of serum creatinine concentration from 133 to 226 mmol/L (i.e. from 1.5 to 2.5 mg/dl).[61] In 2015, the International Club of Ascites (ICA) updated the definition of acute kidney injury (AKI) in patients with liver cirrhosis, which refers to an increase in serum creatinine concentration ⩾0.3 mg/dl (i.e. ⩾26.5 μmol/L) within 48 h, or a percentage increase in serum creatinine concentration ⩾50% from baseline which is known, or presumed, to have occurred within the prior 7 days.[62] AKI is further classified as three stages. Stage 1: an increase in serum creatinine concentration ⩾0.3 mg/dl (i.e. 26.5 μmol/L) or an increase in serum creatinine concentration ⩾1.5 to 2-fold from baseline. Stage 2: an increase in serum creatinine concentration >2- to 3-fold from baseline. Stage 3: an increase of serum creatinine concentration >3-fold from baseline or serum creatinine concentration ⩾4.0 mg/dl (i.e. 353.6 μmol/L) with an acute increase ⩾0.3 mg/dl (i.e. 26.5 μmol/L) or initiation of renal replacement therapy.[62] ICA further proposed the definition of HRS-AKI,[62] which refers to the progression of AKI into stage 2 or 3 and meets the diagnostic criteria of HRS.[61] Accordingly, HRS is divided into HRS-AKI (type 1 HRS) and HRS-NAKI (type 2 HRS).[63] Even so, current evidence regarding terlipressin for the treatment of HRS is mostly based on traditional HRS classification.

Terlipressin can reduce the concentration of renin in the circulatory system and reduce the synthesis of angiotensin II, thereby increasing renal blood perfusion and glomerular filtration rate. Therefore, it is appropriate for the treatment of HRS.[60,64,65] Notably, institution of evidence-based protocol can be translated into improved survival of HRS patients.[66] Until now, at least 20 meta-analyses[67–86] and 20 RCTs[87–106] have explored the efficacy of terlipressin for HRS. Generally, their conclusions are that terlipressin can significantly improve renal function and outcomes of type 1 HRS patients as compared to untreated or placebo and that terlipressin is significantly beneficial for the improvement of HRS as compared to octreotide and midodrine plus octreotide, but had similar mortality and incidence of adverse events as compared to norepinephrine, dopamine, octreotide, and midodrine plus octreotide. Regardless, in real-world clinical practice, terlipressin may be the most widely used vasoactive drug for the treatment of HRS with a higher rate of response to mild kidney injury.[107]

Currently, the EASL guideline recommend that the initial dosage of terlipressin in HRS patients is 0.5–1.0 mg/4–6 h by intravenous boluses; if serum creatinine concentration drops <25% of the baseline value, the maximum dosage can be increased to 2 mg/4–6 h until serum creatinine concentration drops to <133 μmol/L.[25] Recently, an RCT demonstrated that terlipressin given by continuously intravenous infusion was better tolerated than that by intravenous boluses in patients with type 1 HRS and could be equally effective at doses required for continuously intravenous infusion lower than those required for intravenous bolus administration.[108] Considering the drug safety in our clinical practice,[109] we recommend that the starting dosage of terlipressin for HRS is 1–2 mg/12 h by continuously intravenous infusion. The dosage should be adjusted according to the changes in urine output and serum creatinine concentration.

Ascites in liver cirrhosis

Guidance Statement 5. Terlipressin should be considered for severe or refractory ascites in cirrhotic patients, if diuretics are ineffective or patients cannot tolerate diuretic-related adverse reactions.

Ascites in liver cirrhosis is related to visceral vasodilation, activation of renin–angiotensin–aldosterone and sympathetic-adrenal systems, and increased secretion of antidiuretic hormone, which are secondary to portal hypertension.[110] It is also related to low plasma osmotic pressure, which is secondary to reduced hepatic capacity in synthesis of albumin.[110] Management of cirrhotic ascites mainly includes restriction of salt and water, diuretics, paracentesis, peritoneal dialysis, transjugular intrahepatic portosystemic shunt (TIPS), and liver transplantation.[110] Several pilot studies explored the efficacy of terlipressin in cirrhotic patients with non-refractory[111–113] and refractory ascites[113–117] and showed that terlipressin could improve hemodynamic status and increase urine output in cirrhotic patients with ascites. Notably, a multicenter study found that human serum albumin could enhance the vasoconstrictive effect of terlipressin, suggesting the synergistic effect of terlipressin plus human serum albumin for refractory ascites.[115] A questionnaire survey involving 33 gastroenterologists and hepatologists from 30 hospitals in 15 provinces and municipalities in China showed that 29 participants had clinical experiences of using terlipressin in cirrhotic patients with ascites, because the severity of ascites was not improved by diuretics (24/29, 82.76%), renal impairment developed during the use of diuretics (24/29, 82.76%), and urine output was unsatisfactory (6/29, 20.69%).[118] However, no study has evaluated the effect of terlipressin for the prevention of AKI/HRS in cirrhotic patients with ascites but without renal dysfunction.[119] It should be acknowledged that the evidence is extremely lacking. In accordance with the management of HRS, we recommend that the starting dosage of terlipressin for cirrhotic ascites is 1 mg/12 h by continuously intravenous infusion.

Post-paracentesis circulatory dysfunction in liver cirrhosis with ascites undergoing large volume paracentesis

Guidance Statement 6. Terlipressin could be considered for the prevention of post-paracentesis circulatory dysfunction in cirrhotic patients with ascites undergoing large volume paracentesis (>5 L).

Post-paracentesis circulatory dysfunction (PPCD) is defined as an increase in plasma renin activity >50% from baseline within 6 days after large volume paracentesis (LVP), which is defined as the amount of ascites removed is >5 L, in cirrhotic patients with ascites.[120] It is associated with excessive expansion of arterial capillaries after LVP[121] and causes rapid re-accumulation of ascites and development of hyponatremia and renal dysfunction, thereby increasing the mortality.[60,110] Human serum albumin is the first-line choice for the prevention of PPCD.[122] Accordingly, LVP should be performed together with the administration of albumin (8 g/L of ascitic fluid removed) to prevent from PPCD.[110] Several recent studies also suggested that the use of terlipressin could prevent from PPCD. In an RCT, 40 cirrhotic patients with ascites who underwent LVP were assigned to terlipressin ($n = 20$) and albumin ($n = 20$) groups. Terlipressin at a dosage of 1 mg was given by intravenous infusion at the beginning of LVP, 8 h, and 16 h. Plasma renin activity and aldosterone concentrations were significantly improved at 4–6 days after treatment in both terlipressin and albumin groups, and their benefits in preventing from PPCD were similar.[123] Another RCT involving 20 cirrhotic patients with ascites who underwent LVP demonstrated no significant difference in changes of plasma renin activity 4–6 days after treatment between terlipressin and albumin groups ($p = 0.39$).[124] Based on the current evidence, we recommend that the dosage of terlipressin in cirrhotic patients with ascites who will undergo LVP is 1 mg by intravenous boluses at the beginning of the LVP, 8 h, and 16 h.

Bacterial infections in liver cirrhosis

Guidance Statement 7. Terlipressin should be considered in cirrhotic patients with bacterial infections to improve systemic hemodynamic status, microcirculation, and organ perfusion.

Bacterial infections are common in patients with cirrhosis.[125] The prevalence of bacterial infections in cirrhotic patients is 25–35% at admission or during hospitalization[126] with a 4- to 5-fold higher risk than general population.[127–129] The 30-day mortality is 30% and 1-year mortality is 63% in cirrhotic patients with bacterial infections with a 4-fold higher risk of death than those without bacterial infections.[130,131] Spontaneous bacterial peritonitis (SBP) and urinary tract infections are the

most common types of bacterial infections in cirrhotic patients, followed by pneumonia, skin and soft tissue infections, and bacteremia.[126] Antibacterial drugs are the first-line choice of treatment for bacterial infections in cirrhotic patients.[126] It has been reported that terlipressin can cause arterial vasoconstriction, increase blood pressure, and reduce heart rate by activating V_1 receptors, thereby improving hemodynamic status in patients with septic shock.[132,133] Several recent studies suggested that terlipressin be beneficial for bacterial infections in cirrhotic patients with or without shock. In an RCT, 200 cirrhotic patients with SBP and serum bilirubin concentration >4 mg/dl or serum creatinine concentration >1 mg/dl who were treated by antibacterial drugs were randomly assigned to terlipressin ($n=50$), human serum albumin ($n=50$), human serum albumin plus terlipressin ($n=50$), and midodrine ($n=50$) groups.[134] Terlipressin was intravenously infused at a dosage of 1 mg/6 h for 1–3 days. Patients who received terlipressin had significantly lower cardiac output and portal blood flow and higher systemic vascular resistance than those who did not receive terlipressin, but the in-hospital and 30-day mortality were statistically similar among these groups. In another RCT, 84 cirrhotic patients with septic shock were assigned to terlipressin ($n=42$) and norepinephrine ($n=42$) groups.[135] The dosage of terlipressin was adjusted every 15 min to maintain the average arterial pressure of ⩾65 mmHg, and the total dosage was 2–8 mg within 24 h. Terlipressin group had higher rates of MAP >65 mmHg (92.9% *versus* 69.1%, $p<0.01$), survival at 48 h (95.2% *versus* 71.4%, $p<0.01$), and improvement of shock (33.3% *versus* 11.9%, $p=0.02$), and a lower rate of variceal bleeding (0% *versus* 9.5%, $p=0.01$) than noradrenaline group. But the 28-day survival rate was statistically similar between them (26.2% *versus* 14.3%, $p=0.17$). In summary, terlipressin can be added on antibiotic treatment for bacterial infections in cirrhotic patients, and the recommended dosage is 1 mg/6 h by continuously intravenous infusion for 1–3 days. If septic shock develops, the dosage of terlipressin should be adjusted according to the MAP.

Hepatic resection in liver cirrhosis

Guidance Statement 8. Terlipressin can decrease intraoperative portal pressure, blood loss, and amount of blood transfused and postoperative portal pressure in cirrhotic patients undergoing hepatic resection.

Hepatocellular carcinoma, one of the most common malignancies, is often secondary to liver cirrhosis.[136,137] Hepatic resection is a curative treatment for hepatocellular carcinoma.[138] But liver cirrhosis with portal hypertension can significantly increase the risk of complications and deteriorate the outcomes after hepatic resection.[139,140] Terlipressin can decrease perioperative portal pressure in patients undergoing hepatic resection. In an RCT, 50 patients undergoing hepatobiliary surgery were assigned to terlipressin ($n=25$, including 13 patients who underwent hepatic resection) and placebo ($n=25$, including 14 patients who underwent hepatic resection) groups. The initial dosage of terlipressin was 1 mg/30 min by intravenous boluses and then adjusted to 2 μg/kg/h by continuously intravenous infusion until postoperative 4 h. Terlipressin group had significantly lower intraoperative portal pressure (15.96 ± 6.55 mmHg *versus* 16.48 ± 5.04 mmHg, $p<0.05$) and blood loss (842 ± 145.5 ml *versus* 1065.7 ± 202 ml, $p<0.01$), and higher intraoperative MAP (88.7 ± 7.2 mmHg *versus* 83.9 ± 6.98 mmHg, $p=0.02$) than placebo group, but without any significant difference in intraoperative central venous pressure.[141] In another RCT, 84 patients who underwent resection of two or more liver segments were assigned to terlipressin ($n=42$, including 19 patients with liver cirrhosis) and placebo ($n=42$, including 12 patients with liver cirrhosis) groups. The initial dosage of terlipressin was 1 mg/30 min by intravenous boluses and then adjusted to 2 μg/kg/h by continuously intravenous infusion until postoperative 4 h. Terlipressin significantly decreased intraoperative blood loss (1351 ± 887 ml *versus* 1892 ± 889 ml, $p<0.01$) and blood transfusion requirement (30% *versus* 64.2%, $p<0.01$), but increased central venous pressure (8.1 ± 3.6 mmHg *versus* 5.9 ± 3.7 mmHg, $p=0.01$).[142] In a pilot study, 65 patients who underwent resection of three or more liver segments and had portal pressure >12 mmHg were assigned to terlipressin ($n=46$, including 31 patients with liver cirrhosis) and control ($n=19$, including 10 patients with liver cirrhosis) groups. The dosage of terlipressin was 2 mg/24 h by continuously intravenous infusion until postoperative 4 days. Terlipressin could decrease postoperative portal pressure and incidence of liver failure (26% *versus* 53%, $p=0.04$).[143] In addition, in an RCT, 150 patients undergoing major hepatic resection were assigned to terlipressin ($n=75$, including 15 patients with liver cirrhosis) and placebo ($n=75$, including 14 patients

with liver cirrhosis) groups. The initial dosage of terlipressin was 1 mg by continuously intravenous infusion (>2 h), and then adjusted to 1 mg/6 h by continuously intravenous infusion until postoperative 5 days. Terlipressin could not significantly prevent from the development of liver-related complications and AKI (6.5% *versus* 22.6%, $p = 0.15$).[144] Evidence from a meta-analysis also suggested that terlipressin should significantly increase MAP and decrease intensive care unit (ICU) stay in non-cirrhotic patients who underwent hepatic resection.[145] Notably, the dosage of terlipressin was relatively large among these studies, but drug-related adverse reactions had not been clearly reported. In addition, current evidence fails to support the use of terlipressin for the prevention of complications in patients undergoing hepatic resection, despite it can decrease intraoperative portal pressure, blood loss, and amount of blood transfused, and postoperative portal pressure. Therefore, we cannot make a definitive recommendation on the use of terlipressin in patients undergoing hepatic resection.

Liver transplantation in liver cirrhosis

Guidance Statement 9. Terlipressin is considered for the improvement of systemic hemodynamic status and renal function in cirrhotic patients undergoing liver transplantation.

Liver transplantation is a curative treatment approach for advanced liver cirrhosis.[25,146] The incidence of AKI after liver transplantation is 20–90%,[147] which significantly worsens the outcomes of cirrhotic patients.[148–151] Major causes of AKI after liver transplantation include excessive blood loss, hypotension, sepsis, and use of calcineurin inhibitors.[150,151] Screening of preoperative renal function, monitoring of postoperative renal function, and dosage adjustment of calcineurin inhibitors are critical for the prevention of AKI after liver transplantation.[152,153] Terlipressin can improve hemodynamic status and prevent from the development of AKI after liver transplantation. In an RCT, 41 patients with end-stage liver diseases who underwent liver transplantation were assigned to terlipressin ($n = 21$) and saline ($n = 20$) groups.[154] The initial dosage of terlipressin was 1 mg/30 min by intravenous boluses and then adjusted to 2 μg/kg/h by continuously intravenous infusion until postoperative 72 h. Terlipressin group had significantly lower incidence of AKI ($p = 0.04$), smaller drainage volume of ascites ($p < 0.05$), and shorter length of stay ($p = 0.03$). In another RCT, 80 patients with end-stage liver diseases who underwent liver transplantation were assigned to terlipressin ($n = 40$) and control ($n = 40$) groups.[155] The initial dosage of terlipressin was 3 μg/kg/h by continuously intravenous infusion and then adjusted to 1.5 μg/kg/h by continuously intravenous infusion until postoperative 72 h. Terlipressin could significantly increase MAP (47.8 ± 4.8 mmHg *versus* 56.7 ± 6 mmHg, $p < 0.01$) and peripheral vascular resistance (425.0 ± 26.1 mmHg *versus* 723.0 ± 46.8 mmHg, $p < 0.01$) and decrease heart rate (102.6 ± 4.6 *versus* 91.5 ± 5.7, $p < 0.01$), cardiac output (8.8 ± 0.6 *versus* 6.9 ± 0.3, $p < 0.01$), hepatic vascular resistance index (0.73 ± 0.043 *versus* 0.682 ± 0.042, $p < 0.01$), renal vascular resistance index (0.733 ± 0.04 *versus* 0.68 ± 0.05, $p < 0.01$), portal vein blood flow (1807.61 ± 239.62 ml/s *versus* 1402.380 ± 397.26 ml/s, $p < 0.01$), and serum creatinine concentration (1.22 ± 0.31 mg/dl *versus* 1.02 ± 0.29 mg/dl, $p < 0.01$). In addition, in an RCT, 30 patients who underwent living donor liver transplantation were assigned to terlipressin ($n = 15$) and control ($n = 15$) groups.[156] The initial dosage of terlipressin was 1 mg/30 min by intravenous boluses and then adjusted to 2 μg/kg/h by continuously intravenous infusion until postoperative 48 h. Terlipressin group had significantly lower intraoperative portal pressure ($p < 0.01$), postoperative serum creatinine ($p < 0.05$), and postoperative cystatin-C concentration ($p < 0.05$), but higher intraoperative MAP (82.9 ± 11.2 mmHg *versus* 71.3 ± 13.9 mmHg, $p < 0.05$) and intraoperative systemic vascular resistance (736.7 ± 194.2 *versus* 557.2 ± 204, $p < 0.05$) than control group. Based on the current evidence, we suggest that the initial dosage of terlipressin during liver transplantation is 1 mg/30 min by intravenous boluses and then adjusted to 1 mg/12 h by continuously intravenous infusion until postoperative 48–72 h.

Terlipressin-related adverse events

Guidance Statement 10. Terlipressin-related adverse events mainly include gastrointestinal symptoms, electrolyte disturbance, and cardiovascular and respiratory adverse events. They can be often resolved by dosage reduction or drug withdrawal and symptomatic treatment.

Gastrointestinal symptoms

Terlipressin can produce gastrointestinal smooth muscle spasm and visceral vasoconstriction,[157,158]

thereby inducing the development of nausea, abdominal pain, and diarrhea.[85] The incidence of gastrointestinal symptoms during the use of terlipressin is 14–80%.[86,157] Treatment strategy for severe gastrointestinal symptoms mainly includes dosage reduction and even withdrawal and use of antispasmodic drugs. In animal studies, vasopressin-induced gastric smooth muscle spasm can be effectively reversed by local electrical stimulation,[159] but this should be further confirmed by human studies.

Electrolyte disturbance

Terlipressin can activate V_2 receptor, probably producing antidiuretic effect and causing electrolyte disturbance.[160] A case report published in 1998 suggested the risk of developing hypokalemia after terlipressin in cirrhotic patients with gastrointestinal bleeding.[161] Besides, more studies suggested that hyponatremia be a common adverse event of terlipressin in cirrhotic patients. The incidence of serum sodium concentration <130 mmol/L was 0–6%,[162,163] and a decrease in serum sodium concentration of >5 mmol/L was observed in 30–60% of patients treated with terlipressin.[164–167] Patients with better liver function, higher baseline sodium concentration, and longer duration of terlipressin treatment had a higher risk of developing hyponatremia.[168,169] In addition, non-steroidal anti-inflammatory drugs can enhance the reabsorption of water by vasopressin receptors located in the renal tubules by inhibiting prostaglandin synthesis, thereby increasing the risk of terlipressin-induced hyponatremia.[170] Electrolyte disturbance related to the use of terlipressin can be resolved after drug withdrawal. However, severe hyponatremia can worsen the outcome of cirrhotic patients, thus close monitoring of serum sodium concentration is required during the use of terlipressin, and restriction of fluid intake and infusion of hypertonic saline should be considered for the management of hyponatremia, if necessary.[25,171]

Cardiovascular adverse events

Cardiovascular adverse events during the use of terlipressin mainly include myocardial ischemia and arrhythmia, because it can increase cardiac afterload, decrease ejection fraction and cardiac output, and cause bradycardia.[172] Their incidence is estimated to be 11.1%.[85] Management of cardiovascular adverse events includes dosage reduction and withdrawal, except for close monitoring of cardiac function. Continuously intravenous infusion of terlipressin had a lower incidence of cardiovascular adverse events than intravenous boluses.[173] In a previous case report, a cirrhotic patient treated with terlipressin developed sudden tachycardia and chest pain and then was diagnosed with transient left ventricular apical ballooning syndrome based on cardiac enzymes and echocardiographic findings. Symptoms were rapidly relieved after drug withdrawal.[174]

Respiratory adverse events

Respiratory adverse events during the use of terlipressin mainly include dyspnea and respiratory distress,[87,91] because terlipressin can induce pulmonary vasoconstriction, thereby impairing oxygen exchange.[175] Their incidence is estimated to be 10.1%.[85] Recently, in a multicenter RCT involving a total of 300 cirrhotic patients with type 1 HRS, terlipressin group had a higher incidence of respiratory failure than placebo group (10% *versus* 3%), and patients who developed respiratory failure had worse outcome.[106] However, it should be noted that a high dosage of human serum albumin has been employed for type 1 HRS in this RCT. If dyspnea or respiratory failure occurs during the use of terlipressin, the management should include immediate drug discontinuation, oxygen, bronchodilating drugs, and mechanical ventilation, if necessary.

Other adverse events

Terlipressin can also cause skin and subcutaneous tissue ischemia with an incidence of $<5\%$,[176–179] due to its vasoconstrictor effect on the systemic circulatory system.[180] Ischemia often occurs at the head, breast, abdominal wall, small intestine, scrotum as well as extremities.[158,180–184] SBP and alcohol abuse may increase the risk and severity of ischemic complications.[176,185,186] In case of severe ischemic complications during the use of terlipressin, it should be immediately discontinued and vasodilator drugs should be given.[187]

In addition, terlipressin might worsen intracranial edema and pressure in patients with acute liver failure and severe hepatic encephalopathy,[188] probably because it decreased cerebrovascular resistance and increased cerebral blood flow by activating cerebrovascular V_2 receptors.[189] Therefore, its use should be cautious in patients

with acute liver failure and severe hepatic encephalopathy. If intracranial pressure increased during the use of terlipressin, it would be immediately discontinued, and intracranial pressure-lowering drugs would be given.

Unresolved issues

Terlipressin plays an important role in the management of liver cirrhosis–related complications, especially variceal bleeding and HRS. However, the evidence regarding the use of terlipressin in cirrhotic patients with ascites, PPCD, and bacterial infections and in those undergoing hepatic resection and liver transplantation remains insufficient, and high-quality RCTs are needed to further clarify its potential effects. Future well-designed studies should be performed to address several unresolved issues as follows:

1. Renal dysfunction can significantly deteriorate the outcomes of cirrhotic patients with acute gastrointestinal bleeding. RCTs should clarify the effects of terlipressin on renal function and outcomes in cirrhotic patients with acute gastrointestinal bleeding and renal dysfunction.
2. Terlipressin can significantly improve renal function in cirrhotic patients with type 1 HRS, but its survival benefit remains controversial. High-quality studies should clarify the optimal timing of terlipressin and explore whether early use of terlipressin is more beneficial for cirrhotic patients with HRS. In addition, the efficacy of terlipressin for the treatment of severe/refractory ascites in cirrhotic patients and the prevention of renal dysfunction or AKI in cirrhotic patients with severe/refractory ascites should be explored.
3. Postoperative complications are often lethal in cirrhotic patients undergoing hepatic resection and liver transplantation. RCTs should explore the effects of terlipressin on the prevention of complications after hepatic resection and liver transplantation and clarify its optimal dosage and duration.
4. Drug-related adverse events can compromise the use of terlipressin in clinical practice. Monitoring, prevention, and treatment of terlipressin-related adverse events should be further standardized in large-scale real-world studies.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Acknowledgements

None.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Conflict of interest statement

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Availability of data and materials

Data sharing is not applicable to this article as no new data were created or analyzed.

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