BRITISH JOURNAL OF HOSPITAL MEDICINE

REVIEW

The Application of Terlipressin in the Management of Ascites in Liver Cirrhosis: Current Status and Prospects

Lixiao Shen[1], Jie Ying[1], Junbiao Zhao[1,*]

[1]Internal Medicine Department II, Xianju County Traditional Chinese Medicine Hospital, Taizhou, Zhejiang, China
*Correspondence: doczjb_2024@163.com (Junbiao Zhao)

Abstract

Ascites due to liver cirrhosis is a common complication in patients with liver disease, severely affecting their prognosis and quality of life. Traditional treatment methods have significant limitations in managing ascites, highlighting the need for new therapeutic approaches. As an antidiuretic drug, terlipressin has shown good efficacy and potential in treating ascites. This review covers terlipressin's application in managing ascites caused by liver cirrhosis, covering the mechanism of action, usage strategies, clinical effects, and potential side effects. Clinical trial results are discussed to provide a glimpse into the efficacy and safety of terlipressin in managing ascites and its side effects. Additionally, we provide detailed discussions on medication precautions and management strategies for adverse reactions in high-risk patients. Finally, this review outlines future research directions, such as new clinical trial designs, comparisons of terlipressin with other novel drugs, and the exploration of individualized treatment models. These efforts aim to provide references for clinical practice and promote further development in this field.

Key words: terlipressin; liver cirrhosis; ascites; antidiuretic drug; clinical application

Submitted: 3 September 2024 Revised: 10 October 2024 Accepted: 16 October 2024

Introduction

Cirrhosis is a serious liver disease caused by various chronic liver conditions (Valeriani et al, 2023). A notable complication associated with cirrhosis is ascites, which is characterized by the abnormal accumulation of fluid within the abdominal cavity (Xu and Xu, 2019). This condition mainly results from liver dysfunction and increased pressure in the portal vein, known as portal hypertension, which is common in patients with cirrhosis. Ascites is closely linked to increased pressure in the portal vein, the liver's reduced ability to produce proteins, and changes in fluid balance (Tonon and Piano, 2023). In this process, portal hypertension is considered to be one of the main driving factors for the development of ascites in cirrhosis, which is mainly related to the increase of intrahepatic vascular resistance and the decrease of systemic vascular resistance due to the production of endogenous vasodilator substances (Terbah et al, 2024). In patients with decompensated cirrhosis, ascites is a common clinical sign that can significantly affect their quality of life and overall prognosis (Zaccherini et al, 2021). The occurrence of ascites serves as a significant prognostic marker in cirrhosis, with recurrent or refractory ascites

How to cite this article:
Shen L, Ying J, Zhao J. The Application of Terlipressin in the Management of Ascites in Liver Cirrhosis: Current Status and Prospects. Br J Hosp Med. 2024. https://doi.org/10.12968/hmed.2024.0606

often indicating a deterioration in the patient's health status (Miyamoto et al, 2023). Thus, ascites is a major complication of cirrhosis and a marker for liver dysfunction progression. Therefore, the early identification and management of ascites are vital for improving patient survival rates and enhancing their quality of life. Nevertheless, conventional therapeutic approaches such as diuretics and paracentesis may exhibit limited efficacy in instances of refractory ascites. At the same time, although sodium restriction and diuretics remain the cornerstones of ascites management, many patients still require additional treatment when they fail to respond to such medications (Hou and Sanyal, 2009).

Terlipressin is a synthetic vasopressin analogue that has demonstrated significant efficacy in treating ascites caused by liver cirrhosis in recent years (Liu et al, 2019). It exerts its antidiuretic effect by stimulating vasopressin receptors in the splanchnic circulation and renal tubules, leading to splanchnic vasoconstriction and improved renal perfusion (Scheinberg et al, 2023). Additionally, terlipressin can improve renal function and increase urine output, giving it a unique advantage in treating complications related to liver cirrhosis (Kulkarni et al, 2020). Teripressin can also reduce portal inflow by directly and effectively constricting the splenic blood vessels and improving hyperkinetic status. Despite its benefits, caution is warranted when using terlipressin due to potential side effects, including cardiovascular events and electrolyte disturbances (Qi et al, 2022).

This review details the application of terlipressin in managing ascites caused by liver cirrhosis, covering the mechanism of action, usage strategies, clinical effects, and potential side effects. First, we review the antidiuretic effects of terlipressin and its impact on the vascular system and renal function. Next, we summarize the clinical applications of terlipressin in ascites due to liver cirrhosis and its impact on ascites improvement indicators, with reference to clinical trial results, medication regimens, and dosage adjustments, as well as the effect of its combination with other treatment methods. Finally, we discuss the safety and side effects of terlipressin and propose future research directions and challenges.

In summary, the application of terlipressin in the management of ascites due to liver cirrhosis has significant clinical value, but its use requires caution. Through a comprehensive review of its mechanisms, clinical effects, and safety, we hope to provide valuable references for clinical practice and guide future research directions. Next, this review will delve into the specific applications of terlipressin in the management of ascites due to liver cirrhosis.

Application Status and Prospects of Terlipressin in the Treatment of Ascites in Liver Cirrhosis

Chemical Structure and Pharmacological Properties of Terlipressin

Structure and Chemical Characteristics

Terlipressin ($C_{52}H_{74}N_{16}O_{15}S_2$; molecular weight = 1227.37) is a synthetic derivative of the antidiuretic hormone, vasopressin, featuring comparable pharmacodynamic effects to arginine vasopressin. Due to the higher selectivity of its receptor (i.e., V1 receptor) and longer half-life, terlipressin takes an extended period

of time to be excreted from the body. Thus, it can be administered intermittently and has a longer-lasting effect than other vasoconstrictors (Al-Saadi et al, 2022). It is composed of a cyclic peptide made up of eight amino acids, with lysine as the eighth amino acid and a triglycyl group at the N-terminus formed by three glycine residues. After administration, terlipressin is metabolized proteolytically to form its active metabolite, lysine vasopressin. This metabolite mediates the drug's pharmacological effects and has an average plasma half-life of 24 ± 2 minutes (Qi et al, 2022).

Overview of the Functions of Vasopressin V1 and V2 Receptors

The vasopressin receptors, V1 and V2, are G protein-coupled receptors that play important physiological roles. V1 receptors are mainly found in vascular smooth muscle, liver, spleen, and platelets. They contribute to vasoconstriction, hepatic glycogenolysis, and platelet aggregation, playing a significant role in regulating blood pressure and glucose homeostasis. Conversely, V2 receptors are primarily located in the basolateral membrane of the renal distal tubule and collecting duct cells. Vasopressin-induced water reabsorption is mediated by inducing intracellular cyclic adenosine monophosphate (cAMP) production in collecting duct cells, thereby regulating renal antidiuretic functions and body water balance, and promoting the proliferation and migration of renal cells (Jamil et al, 2018). By acting on these two receptor types, terlipressin stimulates the G-protein-coupled receptor cascade, resulting in intracellular calcium inflow to trigger actin-myosin cross bridging, which stimulates smooth muscle vascular contraction and promotes antidiuretic functions (Scheinberg et al, 2023).

Mechanism of Action of Terlipressin

Antidiuretic Effect

Terlipressin, a synthetic analogue version of vasopressin, exhibits potent antidiuretic effects. It primarily activates V1 receptors, leading to vasoconstriction in vascular smooth muscle, which increases vascular resistance and blood pressure (Gonzalez et al, 2020). In patients with ascites due to liver cirrhosis, terlipressin significantly improves renal function by increasing glomerular filtration rate and renal blood flow (Datta et al, 2020). In addition, terlipressin lowers plasma renin activity and aldosterone levels. This reduces the activation of the renin-angiotensin-aldosterone system, further reduces sodium and fluid retention, improves ascites, and controls hepatic hydrothorax. This action inhibits the kidneys' reabsorption of sodium and water, helping to decrease ascites formation (Belcher et al, 2022). Together, these mechanisms allow terlipressin to effectively manage ascites caused by liver cirrhosis.

Effects on the Vascular System

Terlipressin activates V1 receptors, causing vasoconstriction in vascular smooth muscle, which increases vascular resistance and blood pressure. This effect is not limited to the kidneys but also affects the splanchnic vascular system, leading to reduced splanchnic blood flow and increased effective circulating blood volume

(Glavaš et al, 2022). In patients with liver cirrhosis, terlipressin improves hepatic hemodynamics by reducing splanchnic vasodilation, and significantly lowering portal pressure (Garcia-Tsao et al, 2024). Furthermore, terlipressin boosts systemic vascular resistance, enhances circulatory function in liver cirrhosis patients, and helps reduce ascites formation (Terbah et al, 2024). These effects on the vascular system highlight the clinical significance of terlipressin in the treatment of ascites due to liver cirrhosis. In addition, by activating the V1 vasopressin receptor, terlipressin has also been shown to cause oesophagal muscle contraction and pressure on oesophagal varices to help slow down acute varicose haemorrhage (VH). Therefore, terlipressin is one of the drugs that can be combined with vasoactive drugs for treating acute VH, and its efficacy resembles that of octreotide, as proven by many experiments (Scheinberg et al, 2023).

Mechanisms Affecting Renal Function

Terlipressin affects renal function through various mechanisms, significantly improving the prognosis of patients with cirrhotic ascites. First, it improves renal function by increasing renal blood flow and glomerular filtration rate (Chiang et al, 2019). Second, terlipressin inhibits the kidneys' reabsorption of sodium and water by reducing plasma renin activity and aldosterone levels, thereby decreasing the formation of ascites (Bai et al, 2020). Additionally, terlipressin improves the circulatory function of patients with cirrhosis by reducing visceral blood flow and increasing effective circulating blood volume (Garcia-Tsao et al, 2024). Terlipressin's mechanisms of action highlight its crucial role in treating cirrhotic ascites, which leads to significant improvements in patient outcomes. This drug is widely used to manage hepatorenal syndrome, with about 40% of patients showing a reversal of hepatorenal syndrome-acute kidney injury (Wong, 2024).

Clinical Application of Terlipressin in Cirrhotic Ascites and Comparison of Its Efficacy with Traditional Diuretics

Traditional Therapeutic Role of Diuretics and Their Limitations

Diuretics are crucial for treating ascites, and furosemide and torsemide are the most commonly used medications (Kehrenberg and Bachmann, 2022). However, these traditional diuretics have limitations. They can cause problems like drug resistance, worsening kidney function, and electrolyte imbalances (Zaccherini et al, 2021). Specifically, adverse effects of diuretic use or abuse include functional kidney failure, hyponatrium, and hypokalemia (Bartoli et al, 2017). In the event of deterioration, higher doses of diuretics are often needed to manage ascites, thus increasing the risk of side effects. Additionally, diuretics may not effectively relieve the symptoms of ascites, which may negatively impact patients' overall quality of life. This may be related to compensatory mechanisms triggered by the kidney under the guidance of the homeostasis system, where the kidney counteracts the effects of diuretics by achieving more complete reabsorption due to the activation of powerful sodium retention mechanisms. This could eventually counter, or even eliminate, the effectiveness of diuretics (Bartoli et al, 2017).

Comparison of the Efficacy between Terlipressin and Diuretics

Terlipressin works differently from conventional diuretics like furosemide. It significantly increases water reabsorption in the renal tubules and helps prevent the buildup of ascites. Research shows that terlipressin significantly improves survival rates and quality of life for patients, especially for those who do not respond well to standard diuretics (Xing et al, 2019). Moreover, in patients with advanced cirrhosis, renal impairment is more persistent and ascites becomes refractory because it no longer responds to diuretic treatment. A study by Scheinberg et al (2023) found that the addition of terlipressin to conventional treatment can significantly increase the mean arterial pressure, increase 24-hour urine volume, improve renal function, and promote ascites resolution in patients with refractory cirrhosis; comparatively, the combined effect is more pronounced in patients with acute kidney injury (AKI), with less adverse reactions (Scheinberg et al, 2023). The administration of terlipressin with albumin as a treatment to overcome the reduced effectiveness of diuretic treatment has gradually become one of the main commonly used methods to reduce kidney failure, which will be discussed in more details later. At the same time, other studies have further speculated that albumin may help counteract the negative effects of systemic vasodilation by enhancing the vasoconstriction response of terlipressin (Fimiani et al, 2011; Gentilini et al, 2002; Xing et al, 2019). Additionally, terlipressin has shown high effectiveness in treating other complications associated with liver cirrhosis (Kulkarni et al, 2020), such as hepatorenal syndrome, refractory ascites, and acute variceal bleeding. For example, terlipressin is now the treatment of choice for hepatorenal syndrome (Pipili and Cholongitas, 2014). Therefore, comparing terlipressin with traditional diuretics reveals its superior effectiveness in certain patient groups, highlighting the need to tailor treatment strategies to each patient's specific situation.

Overview of Clinical Trial Results

Multiple studies have validated the use of terlipressin in managing cirrhotic ascites. A systematic review by Bai et al (2020) found that terlipressin significantly improved hemodynamic parameters in patients with non-refractory ascites. This included a reduction in heart rate and cardiac output, along with an increase in mean arterial pressure and systemic vascular resistance (Bai et al, 2020). In patients with refractory ascites, terlipressin significantly improved renal function, by increasing glomerular filtration rate, renal blood flow, urinary sodium excretion, and urine output, while reducing serum creatinine levels (Scheinberg et al, 2023). Furthermore, terlipressin demonstrated significant effects in preventing circulatory dysfunction after paracentesis (Bai et al, 2020). These findings indicate that terlipressin plays an important role in improving hemodynamics and renal function in patients with cirrhotic ascites.

Dosage Regimen and Adjustment

Varying dosage regimens and adjustments for terlipressin have been reported in different studies. A review by Kulkarni et al (2020) summarized that terlipressin is usually given in intravenous injection, starting with a dose of 1–2 mg every 4–6

hours. In some studies, terlipressin has also been used for continuous infusion to maintain stable drug concentrations (Bui et al, 2020). Continuous infusion not only enhances the drug's efficacy but also reduces the occurrence of adverse reactions (Weinberg et al, 2023). During treatment, it is necessary to adjust the dosage in a timely manner based on the patient's clinical response and adverse reactions. For patients showing significant improvement in renal function, the dose of terlipressin can be gradually reduced until discontinuation.

Combined Use with Other Treatment Methods

Terlipressin is frequently combined with other treatments to improve efficacy in managing cirrhotic ascites. Research by Sharma et al (2020) demonstrated that combining terlipressin and albumin significantly improved the recovery rate of renal function in patients with refractory ascites. Additionally, terlipressin can be used in conjunction with diuretics to enhance diuretic effects and reduce the accumulation of ascites (Xing et al, 2019). These combination treatment regimens not only enhance the efficacy of terlipressin but also reduce the limitations and adverse reactions associated with monotherapy (Qi et al, 2022). In line with the previous discussion, combination treatment regimens also streamline drug therapy management for patients with refractory ascites complicated by hepatorenal syndrome.

Indicators of Ascites Improvement

The efficacy of terlipressin in managing cirrhotic ascites is primarily assessed by measuring indicators of ascites improvement. A previous study has shown that terlipressin significantly reduces ascites formation through its potent vasoconstrictive effects. In a clinical trial, patients receiving terlipressin showed a significant reduction in ascites volume, and the recurrence rate of ascites was also significantly lower (Xing et al, 2019). Furthermore, terlipressin helps resolve ascites by improving renal function and increasing urine output. These findings indicate that terlipressin has significant efficacy in ascites management, effectively improving patients' clinical symptoms and quality of life (Bai et al, 2020).

Safety and Side Effects of Terlipressin

Analysis of Common Side Effects

Abdominal pain, skin discolouration, intestinal ischemia, cardiac ischemia, cyanosis, bradycardia, and diarrhoea are recognized potential adverse effects of terlipressin. The common adverse effects of terlipressin primarily include gastrointestinal disturbances, electrolyte imbalances, and negative effects on the cardiovascular and respiratory systems. These side effects often improve with a reduction in dosage, cessation of the medication, or through symptomatic management. Gastrointestinal issues are very common, occurring in 14% to 80% of patients (Israelsen et al, 2017), and include symptoms such as abdominal discomfort, diarrhoea, nausea, and vomiting (Allegretti et al, 2017). These reactions are mainly caused by spasms in the gastrointestinal smooth muscle or visceral vasoconstriction triggered by terlipressin (Furgala et al, 2011). Another significant adverse effect is hyponatremia, which occurs in 30% to 60% of patients when serum sodium levels drop

by more than 5 mmol/L during treatment (Qi et al, 2022; Xu et al, 2020). This phenomenon is likely associated with the activation of renal V2 receptors by terlipressin, resulting in antidiuretic effects (Alukal et al, 2020). Additionally, terlipressin may induce cardiovascular complications, including myocardial ischemia and arrhythmias, potentially arising from increased cardiac afterload, diminished ejection fraction, bradycardia, and reduced cardiac output (Krag et al, 2010), with an occurrence rate of 11% (Allegretti et al, 2017). The frequency and severity of these complications depend on the dosage and duration of treatment, underscoring the necessity for vigilant monitoring of patient responses and appropriate dosage adjustments. Despite these potential adverse effects, terlipressin remains a valuable treatment option for managing ascites due to liver cirrhosis. Most side effects can be effectively managed in clinical practice.

Medication Precautions for High-Risk Patients

When using terlipressin to treat ascites caused by cirrhosis, prioritizing the safety of high-risk patients is essential. High-risk patients include those with previous heart issues, liver and kidney problems, or serious electrolyte imbalances. For these patients, terlipressin may cause serious side effects. A previous study has shown that patients with low oxygen levels, particularly those with hepatorenal syndrome type 1 and grade 3 acute-on-chronic liver failure, face a higher risk of respiratory failure and death when treated with terlipressin (Wong et al, 2022). Furthermore, patients experiencing hyponatremia may encounter exacerbated declines in sodium levels, potentially leading to neurological manifestations and grave complications (Meng et al, 2019). Thus, it is vital to conduct thorough risk assessments for these patients. Additionally, careful monitoring of their heart activity, blood pressure changes, and electrolyte levels is necessary throughout treatment. In summary, the formulation of individualized treatment strategies for high-risk patients is critical, coupled with vigilant oversight, to ensure the safety and efficacy of terlipressin therapy.

Management Strategies for Adverse Reactions

Clinicians should use several strategies to effectively manage terlipressin's adverse reactions. First, clinicians should assess the patient thoroughly before starting the medication to identify underlying diseases and potential risk factors. During treatment, it is crucial to monitor the patient's clinical symptoms and lab results closely to identify and address adverse reactions promptly. For example, for patients experiencing gastrointestinal adverse reactions, dosage adjustments or symptomatic treatment may be considered; for cardiovascular adverse reactions such as hypertension and arrhythmias, management can be achieved by adjusting the terlipressin dosage or co-administering other medications. Furthermore, patient education is also an important aspect of managing adverse reactions; doctors should explain the potential risks and precautions of the medication to patients and guide them to seek medical attention promptly if discomfort occurs. Through these comprehensive measures, the adverse reactions of terlipressin can be minimized, thereby enhancing the safety of treatment and patient compliance.

Future Research Directions and Challenges

New Clinical Trial Designs

Terlipressin has demonstrated significant clinical effects in managing ascites caused by liver cirrhosis. However, more clinical trials are needed to optimize its usage strategies and assess long-term efficacy. Future clinical trials should focus on multi-center, large-scale randomized controlled trials to enhance the reliability and generalizability of the findings. Additionally, these trials need to compare different dosages and administration regimens to find the best treatment plan. Inter-patient differences, such as age, gender, and severity of the condition, should also be considered in the trials to develop personalized treatment strategies. Through these studies, a more comprehensive understanding of the mechanism of action and clinical effects of terlipressin can be achieved, providing a more scientific basis for clinical applications.

Comparison of Terlipressin with Other New Drugs

However, ongoing advancements in medical research have led to the emergence of new drugs. Thus, future research should compare the efficacy and safety of terlipressin with other emerging drugs for treating ascites caused by liver cirrhosis (Berger et al, 2024; Bukofzer et al, 2023; Fernández-Varo et al, 2016). For instance, a study comparing terlipressin with drugs like midodrine, octreotide, and norepinephrine has clarified its advantages and disadvantages in various treatment regimens (Reddy et al, 2024). Additionally, the effects of combining terlipressin with other medications should be explored to enhance treatment efficacy and reduce side effects (Israelsen et al, 2020). These comparative studies would reveal more treatment options for clinicians, which potentially improve patient outcomes and quality of life.

Exploration of New Indications

The clinical applications of terlipressin are expanding beyond its traditional role in managing hepatorenal syndrome, attracting considerable interest for its potential use in various other medical conditions. A recent study has suggested that terlipressin may aid in liver regeneration and enhance liver function, opening new research opportunities to explore its protective effects after liver surgeries (Jo et al, 2021). Additionally, research has shown that using terlipressin alongside careful fluid management can significantly reduce the risk of acute kidney injury caused by hemorrhagic shock, offering a new perspective on its role in treating critically ill patients (Castro et al, 2022). As we look ahead, it is crucial for researchers to investigate the therapeutic potential of terlipressin in cases of renal injury, septic shock, and related conditions, and to assess its safety and effectiveness to uncover further clinical applications.

Exploration of Individualized Treatment Models

Personalized treatment is becoming increasingly important in modern medicine, particularly for managing ascites caused by cirrhosis. This requires thorough research into tailored treatment approaches that use terlipressin. A key part of these

personalized models is developing selection criteria for patients who will receive terlipressin. It is essential to assess the patient's pre-existing conditions, comorbidities, and liver function. Research indicated that liver impairment significantly impacts the efficacy and safety of terlipressin (Wong et al, 2022). Additionally, factors like age, sex, and biochemical indicators, such as serum sodium levels, are key determinants of how well a patient responds to treatment. By establishing a robust set of criteria for patient selection, we can improve the success rates and safety profiles associated with terlipressin therapy. Specific biomarkers may serve to identify individuals who exhibit heightened responsiveness to terlipressin, thereby enhancing treatment outcomes (Heinrich et al, 2023). Furthermore, it is vital to explore the optimal timing and dosage of terlipressin across different disease stages to maximize therapeutic effectiveness while minimizing adverse effects. Through the investigation of personalized treatment paradigms, we can devise more tailored therapeutic strategies for patients, ultimately improving clinical outcomes and heightening patient satisfaction. Fig. 1 illustrates the formulation of terlipressin regimens for ascites due to cirrhosis based on different clinical conditions.

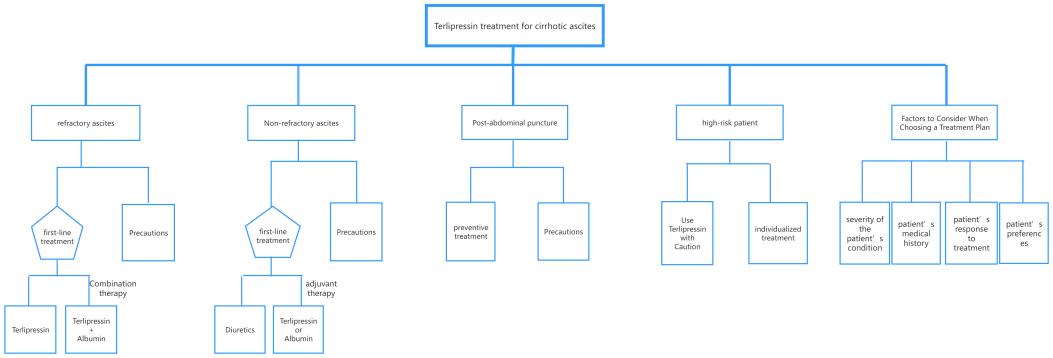

Fig. 1. Formulation of terlipressin regimen for ascites due to cirrhosis based on different clinical conditions.

Conclusion

Terlipressin is highly effective in treating ascites caused by liver cirrhosis by virtue of its unique mechanisms of action, including antidiuretic effects, vascular system modulation, and renal function regulation. Clinical trials show that terlipressin significantly reduces ascites symptoms and improves patient survival and quality of life. However, the clinical use of terlipressin needs to be improved in certain aspects, such as addressing individual patient differences, managing potential side effects, and developing careful medication strategies for high-risk patients to avoid serious complications. Therefore, healthcare providers should establish strict monitoring protocols. They should also customize dosages and create combination therapies that cater to each patient's unique needs to ensure maximum therapeutic effectiveness.

Future research should prioritize developing new clinical trials to thoroughly assess the efficacy and safety of terlipressin, especially in liver cirrhosis patients.

Additionally, comparative studies with other new medications are essential to identify the most effective treatment strategies. Furthermore, the exploration of personalized treatment frameworks is crucial for forthcoming investigations, with the objective of creating therapeutic plans that more precisely cater to patients' individual needs through precision medicine. In summary, despite the challenges in the treatment of cirrhotic ascites, terlipressin has remarkable efficacy and favorable safety profile, which make it a promising therapeutic option. With the continuous advancement of research and the accumulation of clinical insights, terlipressin will play an increasingly significant role in the management of ascites due to liver cirrhosis.

Key Points

- Ascites is a common complication in patients with cirrhosis, significantly impacting their quality of life. The limitations in traditional treatments, such as diuretics and paracentesis, underscore the need for new therapeutic approaches.
- Terlipressin, an antidiuretic drug, has shown promising efficacy in treating cirrhotic ascites. Despite its benefits, caution should be exercised when using terlipressin due to potential side effects that it causes, including cardiovascular events and electrolyte disturbances.
- Future research should focus on developing personalized treatment strategies involving the use of terlipressin, comparing its efficacy with other new drugs, and identifying new indications.

Availability of Data and Materials

All the data of this study are included in this article.

Author Contributions

LXS, JY and JBZ conceived and collaborated on the project. LXS drafted the manuscript. All authors contributed to editing the manuscript and suggesting key revisions to the body of the text. All authors contributed to important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgement

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

References

Allegretti AS, Israelsen M, Krag A, Jovani M, Goldin AH, Schulman AR, et al. Terlipressin versus placebo or no intervention for people with cirrhosis and hepatorenal syndrome. The Cochrane Database of Systematic Reviews. 2017; 6: CD005162. https://doi.org/10.1002/14651858.CD005162.pub4

Al-Saadi A, Sushko K, Bui V, van den Anker J, Razak A, Samiee-Zafarghandy S. Efficacy and Safety of Vasopressin and Terlipressin in Preterm Neonates: A Systematic Review. International Journal of Environmental Research and Public Health. 2022; 19: 13760. https://doi.org/10.3390/ijerph192113760

Alukal JJ, John S, Thuluvath PJ. Hyponatremia in Cirrhosis: An Update. The American Journal of Gastroenterology. 2020; 115: 1775–1785. https://doi.org/10.14309/ajg.0000000000000786

Bai Z, An Y, Guo X, Teschke R, Méndez-Sánchez N, Li H, et al. Role of Terlipressin in Cirrhotic Patients with Ascites and without Hepatorenal Syndrome: A Systematic Review of Current Evidence. Canadian Journal of Gastroenterology & Hepatology. 2020; 2020: 5106958. https://doi.org/10.1155/2020/5106958

Bartoli E, Rossi L, Sola D, Castello L, Sainaghi PP, Smirne C. Use, misuse and abuse of diuretics. European Journal of Internal Medicine. 2017; 39: 9–17. https://doi.org/10.1016/j.ejim.2017.01.016

Belcher JM, Parada XV, Simonetto DA, Juncos LA, Karakala N, Wadei HM, et al. Terlipressin and the Treatment of Hepatorenal Syndrome: How the CONFIRM Trial Moves the Story Forward. American Journal of Kidney Diseases. 2022; 79: 737–745. https://doi.org/10.1053/j.ajkd.2021.08.016

Berger O, Choi W, Ko CH, Thompson MP, Avram MJ, Scott DJ, et al. Long-Circulating Vasoactive 1,18-Octadecanedioic Acid-Terlipressin Conjugate. ACS Pharmacology & Translational Science. 2024; 7: 1252–1261. https://doi.org/10.1021/acsptsci.3c00305

Bui TNN, Sandar S, Luna G, Beaman J, Sunderland B, Czarniak P. An investigation of reconstituted terlipressin infusion stability for use in hepatorenal syndrome. Scientific Reports. 2020; 10: 21037. https://doi.org/10.1038/s41598-020-78044-4

Bukofzer S, Harris G, Cable EE. OCE-205 in rats and non-human primates: Pharmacokinetic and pharmacodynamic analysis. Current Research in Pharmacology and Drug Discovery. 2023; 5: 100163. https://doi.org/10.1016/j.crphar.2023.100163

Castro LUC, Otsuki DA, Sanches TR, Souza FL, Santinho MAR, da Silva C, et al. Terlipressin combined with conservative fluid management attenuates hemorrhagic shock-induced acute kidney injury in rats. Scientific Reports. 2022; 12: 20443. https://doi.org/10.1038/s41598-022-24982-0

Chiang CW, Lin YJ, Huang YB. Terlipressin-Induced Peripheral Cyanosis in a Patient with Liver Cirrhosis and Hepatorenal Syndrome. The American Journal of Case Reports. 2019; 20: 5–9. https://doi.org/10.12659/AJCR.913150

Datta A, Yang CR, Limbutara K, Chou CL, Rinschen MM, Raghuram V, et al. PKA-independent vasopressin signaling in renal collecting duct. FASEB Journal: Official Publication of the Federation of American Societies for Experimental Biology. 2020; 34: 6129–6146. https://doi.org/10.1096/fj.201902020

Fernández-Varo G, Oró D, Cable EE, Reichenbach V, Carvajal S, de la Presa BG, et al. Vasopressin 1a receptor partial agonism increases sodium excretion and reduces portal hypertension and ascites in cirrhotic rats. Hepatology. 2016; 63: 207–216. https://doi.org/10.1002/hep.28250

Fimiani B, Guardia DD, Puoti C, D'Adamo G, Cioffi O, Pagano A, et al. The use of terlipressin in cirrhotic patients with refractory ascites and normal renal function: a multicentric study. European Journal of Internal Medicine. 2011; 22: 587–590. https://doi.org/10.1016/j.ejim.2011.06.013

Furgala A, Thor PJ, Maccallum DS, Dobrek L, Matyja A. Terlipressin facilitates gastric and autonomic system dysfunctions in liver cirrhosis. Hepato-Gastroenterology. 2011; 58: 2041–2044.

https://doi.org/10.5754/hge10163

Garcia-Tsao G, Abraldes JG, Rich NE, Wong VWS. AGA Clinical Practice Update on the Use of Vasoactive Drugs and Intravenous Albumin in Cirrhosis: Expert Review. Gastroenterology. 2024; 166: 202–210. https://doi.org/10.1053/j.gastro.2023.10.016

Gentilini P, Vizzutti F, Gentilini A, Zipoli M, Foschi M, Romanelli RG. Update on ascites and hepatorenal syndrome. Digestive and Liver Disease. 2002; 34: 592–605. https://doi.org/10.1016/s1590-8658(02)80094-9

Glavaš M, Gitlin-Domagalska A, Dębowski D, Ptaszyńska N, Łęgowska A, Rolka K. Vasopressin and Its Analogues: From Natural Hormones to Multitasking Peptides. International Journal of Molecular Sciences. 2022; 23: 3068. https://doi.org/10.3390/ijms23063068

Gonzalez AA, Salinas-Parra N, Cifuentes-Araneda F, Reyes-Martinez C. Vasopressin actions in the kidney renin angiotensin system and its role in hypertension and renal disease. Vitamins and Hormones. 2020; 113: 217–238. https://doi.org/10.1016/bs.vh.2019.09.003

Heinrich S, Austgen T, Castven D, Hess M, Labenz C, Kirstein M, et al. Markers of cell death predict therapy response in patients with cirrhosis and hepatorenal syndrome. United European Gastroenterology Journal. 2023; 11: 92–102. https://doi.org/10.1002/ueg2.12337

Hou W, Sanyal AJ. Ascites: diagnosis and management. The Medical Clinics of North America. 2009; 93: 801–17, vii. https://doi.org/10.1016/j.mcna.2009.03.007

Israelsen M, Dahl EK, Madsen BS, Wiese S, Bendtsen F, Møller S, et al. Dobutamine reverses the cardiosuppressive effects of terlipressin without improving renal function in cirrhosis and ascites: a randomized controlled trial. American Journal of Physiology. Gastrointestinal and Liver Physiology. 2020; 318: G313–G321. https://doi.org/10.1152/ajpgi.00328.2019

Israelsen M, Krag A, Allegretti AS, Jovani M, Goldin AH, Winter RW, et al. Terlipressin versus other vasoactive drugs for hepatorenal syndrome. The Cochrane Database of Systematic Reviews. 2017; 9: CD011532. https://doi.org/10.1002/14651858.CD011532.pub2

Jamil K, Pappas SC, Devarakonda KR. In vitro binding and receptor-mediated activity of terlipressin at vasopressin receptors V_1 and V_2. Journal of Experimental Pharmacology. 2018; 10: 1–7. https://doi.org/10.2147/JEP.S146034

Jo HS, Park HJ, Choi YY, Seok JI, Han JH, Yoon YI, et al. Portal modulation effects of terlipressin on liver regeneration and survival in a porcine model subjected to 90% hepatectomy. American Journal of Translational Research. 2021; 13: 5880–5891.

Kehrenberg MCA, Bachmann HS. Diuretics: a contemporary pharmacological classification? Naunyn-Schmiedeberg's Archives of Pharmacology. 2022; 395: 619–627. https://doi.org/10.1007/s00210-022-02228-0

Krag A, Bendtsen F, Mortensen C, Henriksen JH, Møller S. Effects of a single terlipressin administration on cardiac function and perfusion in cirrhosis. European Journal of Gastroenterology & Hepatology. 2010; 22: 1085–1092. https://doi.org/10.1097/MEG.0b013e320104822

Kulkarni AV, Arab JP, Premkumar M, Benítez C, Tirumalige Ravikumar S, Kumar P, et al. Terlipressin has stood the test of time: Clinical overview in 2020 and future perspectives. Liver International. 2020; 40: 2888–2905. https://doi.org/10.1111/liv.14703

Liu CH, Xing F, Wang J. Research progress of terlipressin in the treatment of cirrhotic ascites-related complications. Chinese Journal of Hepatology. (In Chinese) 2019; 27: 929–932. https://doi.org/10.3760/cma.j.issn.1007-3418.2019.12.005

Meng Q, Dang X, Li L, Liu Z, Li L, Wang H. Severe hyponatraemia with neurological manifestations in patients treated with terlipressin: Two case reports. Journal of Clinical Pharmacy and Therapeutics. 2019; 44: 981–984. https://doi.org/10.1111/jcpt.13031

Miyamoto Y, Honda A, Yokose S, Nagata M, Miyamoto J. The Effects of SGLT2 Inhibitors on Liver Cirrhosis Patients with Refractory Ascites: A Literature Review. Journal of Clinical Medicine. 2023; 12: 2253. https://doi.org/10.3390/jcm12062253

Pipili C, Cholongitas E. Renal dysfunction in patients with cirrhosis: Where do we stand? World Journal of Gastrointestinal Pharmacology and Therapeutics. 2014; 5: 156–168. https://doi.org/10.4292/wjgpt.v5.i3.156

Qi X, Bai Z, Zhu Q, Cheng G, Chen Y, Dang X, et al. Practice guidance for the use of terlipressin for liver cirrhosis-related complications. Therapeutic Advances in Gastroenterology. 2022; 15: 17562848221098253. https://doi.org/10.1177/17562848221098253

Reddy KR, Weinberg EM, Gonzalez SA, Izzy MJ, Simonetto DA, Frederick RT, et al. Safety and efficacy of continuous terlipressin infusion in HRS-AKI in a transplant population. Liver Transplantation. 2024; 30: 1026–1038. https://doi.org/10.1097/LVT.0000000000000399

Scheinberg AR, Martin P, Turkeltaub JA. Terlipressin in the management of liver disease. Expert Opinion on Pharmacotherapy. 2023; 24: 1665–1671. https://doi.org/10.1080/14656566.2023.2244427

Sharma P, Moore K, Ganger D, Grewal P, Brown RS, Jr. Role of Terlipressin and Albumin for Hepatorenal Syndrome in Liver Transplantation. Liver Transplantation. 2020; 26: 1328–1336. https://doi.org/10.1002/lt.25834

Terbah R, Testro AG, Hoermann R, Majumdar A, Chapman B, Gow PJ, et al. Continuous home terlipressin infusion increases handgrip strength and reduces ascites-A prospective randomized crossover study. Hepatology. 2024; 80: 605–620. https://doi.org/10.1097/HEP.0000000000000820

Tonon M, Piano S. Cirrhosis and Portal Hypertension: How Do We Deal with Ascites and Its Consequences. The Medical Clinics of North America. 2023; 107: 505–516. https://doi.org/10.1016/j.mcna.2022.12.004

Valeriani E, Pignatelli P, Senzolo M, Ageno W. Timing of anticoagulation for the management of portal vein thrombosis in liver cirrhosis. Journal of Translational Internal Medicine. 2023; 11: 102–105. https://doi.org/10.2478/jtim-2023-0083.

Weinberg E, Rahematpura S, Gonzalez SA, Izzy MJ, Simonetto DA, Frederick RT, et al. INFUSE: Rationale and design of a multi-center, open label, collaborative study to treat HRS-AKI with continuous terlipressin infusion. Contemporary Clinical Trials Communications. 2023; 36: 101211. https://doi.org/10.1016/j.conctc.2023.101211

Wong F. Terlipressin for hepatorenal syndrome. Current Opinion in Gastroenterology. 2024; 40: 156–163. https://doi.org/10.1097/MOG.0000000000001016

Wong F, Pappas SC, Reddy KR, Vargas H, Curry MP, Sanyal A, et al. Terlipressin use and respiratory failure in patients with hepatorenal syndrome type 1 and severe acute-on-chronic liver failure. Alimentary Pharmacology & Therapeutics. 2022; 56: 1284–1293. https://doi.org/10.1111/apt.17195

Xing F, Li S, Zhang JJ, Sun CY, Huang JR, Gao ZL, et al. Observation of the therapeutic and characteristic effects of terlipressin on refractory cirrhotic ascites. Chinese Journal of Hepatology. 2019; 27: 982–988. (In Chinese) https://doi.org/10.3760/cma.j.issn.1007-3418.2019.12.010

Xu JH, Xu XY. Advances and unmet needs in clinical studies on liver cirrhosis. Chinese Journal of Hepatology. 2019; 27: 913–914. (In Chinese) https://doi.org/10.3760/cma.j.issn.1007-3418.2019.12.001

Xu X, Lin S, Yang Y, Chen Y, Liu B, Li B, et al. Development of hyponatremia after terlipressin in cirrhotic patients with acute gastrointestinal bleeding: a retrospective multicenter observational study. Expert Opinion on Drug Safety. 2020; 19: 641–647. https://doi.org/10.1080/14740338.2020.1734558

Zaccherini G, Tufoni M, Iannone G, Caraceni P. Management of Ascites in Patients with Cirrhosis: An Update. Journal of Clinical Medicine. 2021; 10: 5226. https://doi.org/10.3390/jcm10225226