Current management of refractory ascites in patients with cirrhosis

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Abstract

Liver cirrhosis is a health problem worldwide, and ascites is its principal symptom. Refractory ascites is intractable and occurs in 5%–10% of all patients with ascites due to cirrhosis. Refractory ascites leads to a poor quality of life and high mortality rate. Ascites develops as a result of portal hypertension, which leads to water–sodium retention and renal failure. Various therapeutic measures can be used for refractory ascites, including large-volume paracentesis, transjugular intrahepatic portosystemic shunt, vasoconstrictive drugs, and an automated low-flow ascites pump system. However, ascites generally can be resolved only by liver transplantation. Because not all patients can undergo liver transplantation, traditional approaches are still used to treat refractory ascites. The choice of treatment modality for refractory ascites depends, among other factors, on the condition of the patient.

Introduction

Ascites is one of the most common complications of cirrhosis, along with hepatic encephalopathy (HE), hepatorenal syndrome, and upper gastrointestinal bleeding. Development of ascites is associated with an impaired health-related quality of life and poor prognosis.[1] Approximately 60% of patients with cirrhosis will develop ascites within 10 years after diagnosis of this

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disease.[2] Refractory ascites, which develops in 5%–10% of all patients with cirrhotic ascites, has a high mortality rate.[3] The mean 1-year survival rate of refractory ascites is approximately 50%.[2,4] Ascites can be treated by large-volume paracentesis (LVP), transjugular intrahepatic portosystemic shunt (TIPS), vasoconstrictive drugs, and an automated low-flow ascites pump (ALFApump; Sequana Medical AG, Zurich, Switzerland) system, but liver transplantation is the most effective treatment modality. However, liver transplantation is costly and the number of donors is limited. Moreover, some patients with refractory ascites have contraindications to liver transplantation. This article focusses on current non-transplant treatments for refractory ascites.

Diagnosis and definition

Approximately 75% of ascites cases are due to liver cirrhosis, and other causes include malignancy, cardiac failure, tuberculosis, and pancreatitis.[5] Ascitic fluid is tested to determine the cause of ascites. Ascites is divided into exudates and transudates to facilitate determination of the cause. The serum–ascites albumin gradient (concentration of serum albumin minus that of ascites albumin) is a precise means of detecting ascites. Portal hypertension is associated with a serum–ascites albumin gradient ≥ 11 g/L and inflammation with a gradient of ≤ 11 g/L.[6]

In 1996, the International Ascites Club divided patients with refractory ascites into two subgroups: patients who did not respond to maximum doses of diuretics (diuretic-resistant ascites) and those who developed complications related to diuretic therapy that preclude using an effective dose of diuretic (diuretic-intractable ascites).[7,8] The following criteria for diagnosing refractory ascites were proposed in 2003[9]: 1) treatment duration, intensive diuretic therapy (spironolactone [400 mg/day] and furosemide [160 mg/day]) for at least 1 week with a salt-restricted diet (<5.2 g of salt/day); 2) lack of response, mean weight loss of <0.8 kg over 4 days and a urinary sodium output less than the sodium intake; 3) early recurrence of ascites, reappearance of grade 2 or 3 ascites within 4 weeks of initial mobilization; and 4) diuretic-induced complications, diuretic-induced hepatic encephalopathy (defined as development of encephalopathy without any other precipitating factor). Diuretic-induced renal impairment is defined as an increase in the serum creatinine level of $>100\%$ to a value >2 mg/dL in patients with treatment-responsive ascites. Diuretic-induced hyponatremia is defined as a decrease in the serum sodium level of >10 mmol/L or a serum sodium level of <125 mmol/L. Diuretic-induced hypokalaemia or hyperkalaemia is defined as a change in serum potassium to <3 mmol/L or >6 mmol/L, despite appropriate measures.[9]

Pathophysiology

Portal flow in refractory ascites is constricted because of the presence of cirrhosis and portal hypertension subsequently develops. The widely accepted hypothesis for refractory ascites is that the initial step that leads to ascites is portal hypertension following liver cirrhosis. This leads to an increased release of local vasodilators, such as nitric oxide, leading to vasodilation of splanchnic vessels.[10] In patients with advanced cirrhosis, splanchnic arterial vasodilation decreases the volume of arterial blood volume and makes maintaining blood pressure difficult. Circulatory dysfunction and neurohumoral activation are remarkable in these patients.[11] For compensation of this situation, vasoconstrictors and antinatriuretic factors are activated (e.g., the renin–angiotensin–aldosterone

system and sympathetic nervous system), resulting in sodium and water retention.[11] Intestinal capillary pressure and permeability are affected by vessel vasodilation and portal hypertension, resulting in retained fluid in the abdominal cavity. Marked impairment in renal excretion of free water, renal vasoconstriction, and sodium reabsorption are factors that contribute to developing refractory ascites[12]

Therapies

LVP

LVP, the first-line treatment for refractory ascites, is defined as direct aspiration of >5 L of ascites.[7] Compared with diuretics, LVP can control massive ascites rapidly and shorten the hospital stay,[13,14] but it has no effect on the mortality rate.[15] Removal of a large volume of ascites is associated with paracentesis-induced circulatory dysfunction (PICD),[7] which can be prevented by an infusion of 7–8 g of albumin per litre of fluid tapped.[16] Albumin reduces the mortality rate of massive ascites treated by LVP compared with other plasma expanders.[17] Patients with refractory ascites should continue to receive diuretics if tolerated, unless there are major complications or the urinary sodium level is <30 mmol/day.[9]

Patients with refractory ascites may require repeated paracentesis, which leads to poor compliance, reduces the quality of life, and increases the risk of PICD, bleeding, and infections.[18] Patients with a blood platelet count <50,000/mm^3, Child-Pugh class C, and those suffering from alcoholism are at increased risk of PICD.

The volume and frequency of paracentesis depend on the timing of reappearance of ascites and the severity of this disease. LVP remains the first-line therapy for refractory ascites.

TIPS

If four or more paracentesis procedures are performed, or paracentesis is not tolerated or contraindicated, TIPS is recommended.[9] TIPS can relieve refractory ascites by directly reducing portal venous pressure.[19] The most common non-surgical complication of TIPS is development of HE, which occurs in 15%–48% of cases.[20–22] In a large cohort study, patients with TIPS placement experienced significant improvement in renal function, particularly those with a baseline estimated glomerular filtration rate of < 60 mL/min/1.73 m^2, compared with a serial LVP cohort.[23] Whether TIPS increases the survival rate of patients with refractory ascites is controversial.[24–27] A study of 97,063 patients with cirrhosis on a transplant list in the United States suggested that TIPS improved the survival rate;[28] however, the percentage of patients with refractory ascites was unclear.

Two types of stent can be used for TIPS: bare and covered. Bare stents are associated with a high rate of dysfunction of shunts. Stenosis or obstruction of bare stents occurs in 70% of cases within 1 year.[29] In contrast, covered stents, including polytetrafluoroethylene (PTFE)-covered stents, have a lower frequency of dysfunction than do bare stents.[30–32]

The use of covered stents for TIPS in patients with refractory ascites increases the survival rate.[33,34] The volume of blood shunted through the liver is related to post-TIPS HE;[35] therefore, the stent diameter is important. A 10-mm PTFE stent is more effective in controlling refractory ascites than an 8-mm stent, and it does not increase the incidence of HE.[36] Additional studies of stent diameter that take into consideration sex and weight are warranted.

TIPS is associated with an increased incidence of HE. Selection of appropriate patients for TIPS is important to improve the survival rate.[26] In a meta-analysis,[37]

patients older than 65 years who had a history of previous HE and had a Child-Pugh score $\geq$ 10 were more likely to develop post-TIPS HE. The critical flicker frequency before TIPS may predict the occurrence of overt post-TIPS HE.[38] TIPS is not recommended in patients with severe liver disease because of the lack of data on efficacy.[7]

Vasoconstrictive drugs

Several oral drugs are available for treating refractory ascites. These drugs increase the systemic atrial volume by inducing vasoconstriction. Midodrine is an α1-adrenergic agonist that is used in cirrhotic patients with ascites. Midodrine increases the effective arterial blood volume by causing splanchnic vasoconstriction, and it improves renal perfusion and glomerular filtration.[39] The American Association for the Study of Liver Diseases guidelines recommend midodrine for refractory ascites.[40] Clonidine is an α2-adrenergic agonist with effects that are similar to those of midodrine, which theoretically reduces central sympathetic outflow and release of norepinephrine. Clonidine combined with standard medical treatment is effective for controlling ascites.[41,42] Large-scale clinical trials comparing the efficacy of midodrine and clonidine for controlling refractory ascites are required.

Vasopressin V2 receptor antagonists, also known as vaptans, competitively bind and block arginine vasopressin V2 receptors in renal collecting ducts. A meta-analysis showed that vasopressin V2 receptor antagonists were effective for patients with ascites, especially refractory ascites, and functioned by elevating serum sodium concentrations.[43] The US Food and Drug Administration issued a warning for tolvaptan. This was issued because a potential risk of liver injury was identified during a clinical trial of tolvaptan to treat autosomal dominant polycystic kidney disease.[44]

Patients in this previous study who were treated with 120 mg/day of tolvaptan for 3 years showed significantly higher serum bilirubin and alanine aminotransferase levels. However, 120 mg/day of tolvaptan is considerably higher than the tolvaptan dose used to treat patients with cirrhosis. The typical treatment-emergent adverse event caused by vaptans is excessive correction of serum sodium concentrations (>145 mmol/L), which can lead to osmotic demyelination and myelinolysis.[45] Therefore, serum sodium levels should be monitored in patients with ascites who are treated with vaptans.

ALFApump

The ALFApump is a new technology that was introduced for patients with refractory ascites in recent years. This device is subcutaneously implanted and battery-powered, and moves ascites from the peritoneal cavity to the urinary bladder to facilitate removal of fluid by urination.[46] The design of the ALFApump enables it to function in the day time and stop when sleeping. Additionally, this device has internal sensors that monitor the pressure of the bladder and peritoneal cavity. When there is no ascites in the peritoneal cavity or the bladder is full, the ALFApump will stop working. The only inconvenience of this device is that the battery of the system needs charging for less than 20 minutes twice a day.[47] Compared with repeated LVP, the ALFApump is more acceptable for patients with refractory ascites and improves the quality of life.

The ALFApump is mainly used in patients who are unsuitable for TIPS, those who previously failed TIPS, or patients with portal thrombosis. A multicentre study of the ALFApump system showed a significant reduction in the frequency of LVP (median number per month, 3.4 vs 0.2, p < 0.01).[46] A single-centre study, which included

10 patients, showed pump malfunction in 50% of patients.[48] This finding may indicate that selection of patients and surgical technology are crucial. Further study is required on the ALFApump. Two multicentre, randomized, controlled studies by Devabhavi et al.[49] and Bureau et al.[50] showed that there was no difference in survival between patients who were treated with the ALFApump and LVP with a follow-up for 6 and 3 months, respectively. However, clinical trials with large samples are required in the future.

The ALFApump system is potentially a source of infection, which may lead to severe sepsis, acute on chronic liver failure, and hampering of liver transplantation.[51] Therefore, further research on this technology is required. Bellot et al.[46] showed that there was no significant difference in the number of cirrhosis-complications related to the ALFApump in those with or without recommendation of the Data Safety Monitoring Board. This finding suggests that this therapy does not interfere with progression of liver cirrhosis. The ALFApump can be a bridge for patients on the transplant list, but the ultimate solution is still liver transplantation.

Liver transplantation

Liver transplantation can radically reverse portal hypertension. All patients with ascites should be considered as potential candidates for liver transplantation. Patients with refractory ascites, spontaneous bacterial peritonitis, or hepatorenal syndrome should be prioritized based on their Model for End-Stage Liver Disease score.[52,53] There is a remarkable improvement in the survival rate after liver transplantation.[54]

Summary

Ascites can be treated using various modalities, the most effective of which is liver transplantation. Non-transplant modalities are frequently used for this condition because of the small number of donor livers available and the cost of transplantation. Moreover, a means of reducing the incidence of side effects of conventional treatments, including LVP and TIPS, should be investigated. ALFApumps show promise, but they must be evaluated in large-scale, randomized, controlled, multicentre studies.

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