ABSTRACT

Background: Ascites is the pathologic accumulation of fluid within the peritoneal cavity. This condition when refractory to treatment heralds more severe complications and a poor prognosis. The aim of this paper is to review literature on the pathogenesis and current management of refractory cirrhotic ascites.

Methods: An English language literature search using Medline and PubMed (1976-2006March) was done to assess all research/review articles on the pathogenesis and management of refractory cirrhotic ascites.

Results: The onset of ascites in cirrhotic patients signifies poor prognosis. Only a small percentage of patients with cirrhotic ascites develop true resistance to diuretics. Serial therapeutic paracentesis remains the available option for the majority of patients. Liver transplantation is the only definitive therapy, but the use of this method is limited by the availability of the organ and the cost of such procedure. Transjugular intrahepatic portosystemic stent shunt is a useful procedure but limited by the complication of disseminated intravascular coagulopathy. The role of other alternatives is less clearly defined.

Conclusion: Therapeutic options in patient with cirrhotic ascites remains serial therapeutic paracentesis with or without plasma expansion. Transjugular intrahepatic portosystemic stent-shunt is a useful alternative. The unavailability of liver donors serves as a barrier to liver transplantation.

KEYWORDS: Refractory ascites; Cirrhosis; Pathogenesis; Management.

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INTRODUCTION

Ascites is the pathologic accumulation of fluid in the peritoneal cavity. According to a consensus conference of the International Ascites Club, refractory ascites is defined as ascites that cannot be mobilized by diuretics because of a lack of response (mean weight loss less than 200g/d over 4 days), or the development of diuretic-induced complications (such as hyponatremia, hypokalemia, renal impairment, hepatic encephalopathy), precluding an effective diuretic dosage. Ascites is caused by liver cirrhosis in 75% of cases; other causes include congestive cardiac failure, nephrotic syndrome, neoplasia and protein losing enteropathy. Refractory ascites develops in about 10% of cases of liver cirrhosis. Ascites is the most common complication of liver cirrhosis. Within 10 years after the diagnosis of compensated cirrhosis, about 58 percent of patients will have developed ascites. The development of ascites is the final consequence of a series of anatomic, pathophysiologic, and biochemical abnormalities occurring in patients with cirrhosis. Ascites in patients with cirrhosis is a major cause of morbidity and a serious prognostic factor.

Ascites generally presents with abdominal distension as the predominant clinical symptom. Its presence can be demonstrated clinically by the puddle sign, shifting dullness and the fluid thrill. Puddle sign is the most sensitive of all, as it is capable of detecting a few hundred milliliters of ascitic fluid. Shifting dullness demonstrate ascitic fluid exceeding 1 liter while the fluid thrill is only useful in the setting of tense ascites as it is often seen in refractory ascites. The development of refractory ascites in cirrhosis severely affects patient’s prognosis and heralds more severe complications. The later include dyspnoea (due to diaphragmatic splitting), pleural effusion, hypostatic pneumonia and lower lung collapse, multiple hernias (particularly umbilical, femoral, and inguinal), scrotal oedema (and the potential for scrotal sepsis), pre-renal / renal failure, hepatorenal syndrome and spontaneous bacterial peritonitis.

The aim and objectives of this paper are to review available literature and discuss the pathogenesis and the current management of refractory cirrhotic ascites.

Pathogenesis

The development of portal hypertension (PHT) is the first step toward fluid retention in the setting of cirrhosis. Ascites usually does not develop in cirrhotic patient without PHT. Fluid accumulates when a portal pressure of 12mmHg is exceeded. On the other hand, ascites will usually disappear if portal pressure is reduced below 12mmHg e.g. after a surgical...
portosystemic shunt. PHT leads to profound changes in the splanchnic circulation including vascular, functional and biochemical abnormalities that contribute to the pathogenesis of fluid retention. The most recent theory of ascites formation in liver cirrhosis is the arterial vasodilatation hypothesis.

Mechanisms of Vasodilatation

The increased level of circulating vasodilators is the major cause of vasodilatation in cirrhotic patients, although portosystemic collaterals may contribute. Vasodilators that are considered include glucagons, vasoactive intestinal peptide, substance P and prostaglandins. It has been observed in pre-ascitic and ascitic cirrhotic patients that there is an increased level of systemic prostacyclin. However, in advanced liver disease, renal prostacyclin production is reduced resulting in marked renal vasoconstriction.

Recent thinking is focused on the possible role of Nitric oxide (NO) in the splanchnic vasodilatation in cirrhosis. The following observations were advanced to suggest that NO is the primary mediator of vasodilatation in cirrhosis.

1. The serum levels of nitrite and nitrate, an index of in vivo NO synthesis, are significantly higher in cirrhotic patients than in control.
2. There is an increase in activity of NO synthase in the arterial vessels of cirrhotic patients with ascites.
3. The factors responsible for increased NO synthesis in cirrhotic patients have been attributed to absorbed endotoxin from the gastrointestinal tract, which is less efficiently cleared due to portal-systemic shunting and decreased reticular endothelial cell function in cirrhosis.

Consequences of Vasodilatation

Splanchnic arterial vasodilatation leads to increased portal blood flow, which in turn leads to more severe portal hypertension. As a result of vasodilatation, there is activation of endogenous vasoconstrictors, sodium and water retention, and increased renal vasoconstriction.

Cirrhotic vasodilatation results in stimulation of baroreceptors thus resulting in activation of the sodium-retaining neurohumoral mechanisms in an attempt to restore perfusion pressure to normal. The neurohormones involved include the renin-angiotensin system, sympathetic nervous system, and antidiuretic hormone. The secretion of these three hormones is directly proportional to the severity of the haemodynamic disturbances. The net effect of this is avid sodium and water retention.

The presence of sodium retention is indicative of a 50 percent reduction in liver function. It has been shown that the degree of sodium retention is inversely related to survival. Initially in cirrhotic patients, water excretion is usually normal, but with the development of ascites and progressive liver damage, this is impaired. This abnormality is related to inability to suppress antidiuretic hormone (ADH). The inability to excrete water regularly leads to the development of hyponatraemia and hypoosmolality. Thus such patients usually demonstrate urinary sodium retention, increased total body sodium, and dilutional hyponatraemia.

Increased ADH secretion is fairly proportional to the severity of the cirrhosis. The degree of hyponatraemia also parallels the severity of the liver disease, thus, along with the degree of sodium retention, the three are poor prognostic factors in liver cirrhosis.

The renal blood flow is also reduced as a result of activation of the vasoconstrictor systems. Though, renal perfusion is initially maintained by the vasodilators such as prostaglandins and possibly nitric oxide, eventually, the natural progression of liver disease overcomes these protective mechanisms leading to progressive renal hypoperfusions, a gradual decline in the glomerular filtration rate and the hepatorenal syndrome in some patients.

Patients with liver disease may have a clinically masked reduction in glomerular filtration rate and both urea and creatinine production may be reduced as a result of liver disease and decreased muscle mass, leading to a near normal serum creatinine concentration.

THERAPY

Therapeutic Classification

Ascites due to cirrhosis can be mobilized in approximately 90 percent of patients with a treatment regimen consisting of dietary sodium restriction and diuretics; however, 10% of patients do not respond to the above measures or develop complications from diuretic therapy. These patients are classified as having refractory ascites. Prognosis for this subgroup of patient is poor, with a 50% 1-year mortality. A patient is said to be resistant when one or both of the following criteria is present in the absence of therapy with nonsteroidal anti-inflammatory drugs (NSAIDS) which can induce renal vasoconstriction and diminish diuretic responsiveness.
b. Large volume paracentesis (LVP). This involves the removal of between 4-10 liters of ascites fluid over a period of 24 hours. The procedure can be repeated as often as required. Large-volume paracentesis ameliorates the shortness of breath and easy satiety that these patients experience. It may also be important in the reduction of the hepatic venous pressure gradient, intravariceal pressure, and variceal wall tension27. A close monitoring of the patient is however necessary and a commensurate fluid and albumin replacement given (40g of albumin for every 3-5 liters of ascites fluid removed). Intravenous albumin is important in order to avoid renal, electrolyte and haemodynamic complications, which could otherwise arise from the procedure25.

Studies have been done to ascertain whether other colloid preparations will be as effective as salt poor albumin. Planas, Ginas and Arroyo found out that dextran 70 is less efficacious to dextran 40, haemacel, plygeline, normal saline and hydroxyethyl starch. They were however less effective than albumin. It is therefore advisable that the procedure should be carried out when the appropriate colloid solutions are available.

The limitations of this approach are that repeated LVPs cause protein and complement depletion, and may indirectly predispose to ascitic fluid infection27.

c. Total volume paracentesis (TVP):- This technique is similar to large volume paracentesis but involves total drainage of the entire volume of ascites in a single day under close monitoring and intravenous salt poor albumin replacement. Tio, Gines, Arroyo et al observed that TVP compares favourably with surgical shunting as a treatment modality26. An increase in plasma renin activity after paracentesis has been considered as evidence of effective hypovolemia. Postparacentesis plasma volume expansion does help prevent asymptomatic laboratory abnormalities, which are associated with poor prognosis29.
2. Transjugular Intrahepatic Portosystemic Stent Shunt (TIPS).

Percutaneous creation of a transjugular intrahepatic portosystemic shunt (TIPS) through a jugular route connects the hepatic and portal veins in the liver. The goal is to reduce portal pressure and thus prevent variceal bleeding\textsuperscript{30}. The procedure reduces the activity of the renin angiotensin-aldosterone axis and increases natriuresis and GFR, a marked or complete reduction in ascites, and cessation of diuretic therapy or the use of much lower diuretic doses\textsuperscript{31}. A lower plasma creatinine concentration and improved sodium excretion have been observed because TIPS improves renal function and sodium excretion\textsuperscript{30,32,33} and is more effective than paracentesis in removing ascites\textsuperscript{34,35}. Improvement in the nutritional status of the patient and quality of life was also documented\textsuperscript{36}. A randomized controlled trial, which compared TIPS to paracentesis, found that patient mortality was higher in the TIPS group and that the mortality risk was greatest in patients with Child-Pugh class C\textsuperscript{36}. Nevertheless, a recent meta-analysis has reported a tendency toward improved survival with TIPS\textsuperscript{34}. Associated complications of TIPS procedure include hepatic encephalopathy, early thrombosis and delayed shunt stenosis.

3. Liver transplantation

Liver transplantation is indicated in a previously compensated cirrhotic patient who now develops ascites, if there are no contraindications such as active alcohol use. Patients usually progress from diuretic-sensitive to diuretic-resistant ascites over a period of months to years, if they do not die from other complications of cirrhosis\textsuperscript{37}.

Patients should be listed early for liver transplantation at the earliest indication of diuretic resistance; lest they may not live long enough to undergo liver transplantation because of the shortage of the organ.

4. Miscellaneous

a. Peritoneovenous Shunt

A peritoneovenous shunt, which drains into the internal jugular vein, reinfuses ascites into the vascular space. The procedure has been virtually abandoned due to the attendant complications, including, disseminated intravascular coagulation, infection of the shunt, which can lead to bacteraemia, variceal bleeding and small bowel obstruction. Probably the only indication for the peritoneovenous shunt is the rare patient with diuretic-resistant cirrhotic ascites, who is not a candidate for transplantation, and who has too many abdominal surgical scars to permit safe successful paracentesis\textsuperscript{37}.

b. Surgical portosystemic shunts

Surgical portosystemic shunts significantly reduce the hepatic venous pressure gradient, the development of ascites, and the frequency of spontaneous peritonitis\textsuperscript{37}. A small-diameter prosthetic portocaval H-graft has been recently compared to TIPS for the treatment of bleeding oesophageal varies. The surgical group has a greater reduction in venous pressure gradient and lower rates of prosthesis occlusion; the mortality rates were however similar in both groups\textsuperscript{33}.

c. Extracorporeal ultrafiltration and re-infusion

Other available therapeutic options include extracorporeal ultrafiltration and re-infusion. Extracorporeal ultrafiltration of ascitic fluid and intravenous or intraperitoneal reinfusion is an alternative to albumin or synthetic colloid infusion. The Rhodascit machine which is specifically designed for this purpose is however very expensive and hence it is difficult to sustain this treatment modality for protracted periods and the development of disseminated intravascular coagulation with this procedure has decreased enthusiasm for its use\textsuperscript{38}. Jamieson et al described a modification of this technique used in paediatric patients. They utilized a standard Gambro haemofilter to effect ultrafiltration of the ascites before reinfusing the high protein-concentrate back into the patient. The possibility of this should also be explored in the adults particularly for patients who cannot withstand paracentesis because of haemodynamic instability.

d. Novel Drugs

Atrial natriuretic peptide [ANP] normally increases glomerular filtration rate [GFR] and natriuresis. There is reduced natriuretic response to ANP in cirrhosis patients with ascites despite elevated levels\textsuperscript{40}. Exogenous administration of ANP, together with the
splanchnic vasoconstrictor terlipressin to counter the hypotensive effect of ANP increases renal blood flow, GFR and natriuresis in patients with refractory ascites.

e. Dopamine

Studies of dopamine in refractory ascites have failed to show an increase in GFR/diuresis or natriuresis. However, use of docarpine, [an orally active dopamine prodrug] improves ascites control in patients with refractory ascites.

f. Miscellaneous

Other agents that have been tried that may increase diuresis in cirrhotic patients with ascites include Vasopressin-V2-receptor antagonists, OPC-3126, Niravoline, a K-opoid antagonist and the adenosine-1-receptor antagonist FK352. Vasopressin-V2-receptor antagonists mobilize free water and thus might be an excellent alternative or adjunct to diuretic treatment. The efficacy and safety of these new compounds in patients with cirrhosis have recently been demonstrated.

This promising new pharmaceutical concept is currently under investigation in international phase II/III trials. Further studies using these agents may provide further information regarding their efficacy in refractory ascites.

CONCLUSION

The development of ascites portends poor prognosis in cirrhotic patients. About 10% of cirrhotic patients develop resistant ascites. Liver transplantation is the only definitive therapeutic option. Ascites management is important before transplantation, and in those candidates that are not fit for transplantation, serial therapeutic paracentesis is the most widely used option. The current use of TIPS is limited by its complications especially in patients with Child-Pugh class C disease.

REFERENCES


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