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Current Management Strategies For Refractory Ascites, Hepatorenal Syndrome & its Complications: A Review

Medical Science

KEYWORDS : Hepato-renal syndrome(HRS), Refractory ascites, TIPS

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ABSTRACT

Circulatory disturbances seen in advanced cirrhosis leads to development of ascites which can be refractory to diet and medical treatment. This state of refractoriness gets complicated with problems like hydrothorax, spontaneous bacterial peritonitis(SBP), spontaneous empyema thoracic, dilutional hyponatremia and umbilical hernia. The circulatory abnormality may progress to functional renal failure known as Hepato renal syndrome(HRS).
In this article we will discuss the recent management strategies and complications of refractory ascites and hepato-renal syndrome.

INTRODUCTION: Circulatory disturbances seen in advanced cirrhosis leads to development of ascites which can be refractory to diet and medical treatment. This state of refractoriness gets complicated with problems like hydrothorax, spontaneous bacterial peritonitis (SBP), spontaneous empyema thoracic, dilutional hyponatremia and umbilical hernia. The circulatory abnormality may progress to functional renal failure known as Hepato renal syndrome(HRS). Management of refractory ascites is based on procedures like large volume parencentesis and Trans jugular intrahepatic porto systemic shunt(TIPS).

REFRACTORY ASCITES: Diagnostic criteria of refractory ascites are following

- Lack of response to maximal dose of diuretic for at least one week
- Diuretic induced complications in the absence of precipitating factors
- Early recurrence of ascites within 4 weeks of fluid mobilisation
- Persistent ascites despite sodium restriction i.e 50-90 mmol/day
- Mean weight loss <0.8 kg over 4 days
- Urinary sodium excretion less than sodium intake.

Patients of refractory ascites does not respond to maximal dose of diuretic i.e spironolactone 400 mg and frusemide 160 mg for atleast one week. In another case physicians are unable to achieve maximum dose of diuretic due to adverse effects like hypernatremia, hypokalemia, hyperkalemia and hepatic encephalopathy.

In fact on this basis in 1988, the international ascites club divided refractory ascites into 2 categories:

Type I: diuretic resistant ascites &

Type II: Diuretic intractable ascites where full dose of diuretic could not be achieved due to adverse effects of diuretics.

Refractory ascites is one of the most serious sign of decompensated liver disease or of cirrhosis. It has a prevalence rate of 5-10% in patients with ascites and a survival rate as low as 50% at 6-12 months post diagnosis.

Refractory ascites isw associated with other complications which will increase the morbidity and mortality like dilutional hyponatremia, SBP, spontaneous empyema thoracis, hydrothorax and Hepato renal syndrome(HRS).

PATHOPHYSIOLOGY: Following factors together act to produce refractory ascites and complications:

Splanchnic vasodilation:
Portal hypertension along with the release of various vasodilators like PGE1, prostacycline and nitric oxide in splanchnic circulation causes splanchnic vasodilation.

Dilated splanchnic circulation along with portal hypertension causes elevated sinusoidal pressure which in turn causes increase in venous blood flow. This is turn causes increased lymph formation in splanchnic circulation. The rate of lymph production exceeds the flow rate in thoracic duct. Hence fluid leaks into the peritoneal cavity forming ascites.

Arterial system under filling:
Splanchnic vasodilation causes shunting of blood volume towards splanchnic circulation resulting in arterial system under filling. This is turn causes activation of the renin-angiotensin-aldosterone system(RAAS) and the sympathetic nervous system(SNS). This is turn causes sodium and water retention to compensate for arterial under filling but eventually body is unable to maintain homeostasis and more fluid in shifted towards splanchnic circulation which then shifts into peritoneal cavity forming ascites but arterial system remains under filled. This also explains the development of dilutional hyponatremia.

Due to activation of RAAS and SNS system Angiotensin II and norepinephrine is released which causes vasoconstriction, renal hypo perfusion and decreases GFR. This in turn reduces vasodilator production (PGE2,Nitric oxide etc) in renal vascular bed. This explains the development of Hepato renal syndrome.

PROGNOSIS: Refractory ascites is associated with high mortality rate with rate as high as 50% at 6-12 months post diagnosis. Indeed the survival rate in patient with normal liver function and normal serum sodium could be as high as 80% at 3 years. But mortality rate depends upon the presence or absence of the following factors:

Bad prognostic factors	Good prognostic factors
Age between 50-60 years, Diabetes, heavy alcohol,hepatocellular carcinoma	Normal liver function
Hepatorenal syndrome(HRS I>HRS II), Spontaneous bacterial peritonitis, hepatic hydrothorax, spontaneous bacterial empyema	Normal sodium level

MANAGEMENT:

Restricted sodium diet(<90 mmol/day): First patient should be evaluated for the compliance with restricted sodium diet by collecting 24 hrs urine or recording urine sodium to potassium ratio and daily weight recording.

Diuretic: First spironolactone 100 mg/day is tried.If no response in 3-4 days then gradually increase the dose to 400 mg/day. Again if no response, add frusemide 40 -160 mg/day and increase spironolactone to 600 mg/day. If yet no response then case is called refractory ascites. During diuretic therapy daily body wight loss should be limited to 0.5 kg/day to avoid hypovolemia. Free water restriction is controversial because it may cause hypovolemia, thus it further stimulates RAAS.

Large volume Parancentesis: The quality of life as well as survival rate of patient with refractory ascites has little or no improvement with only diuretic treatment. So large volume parancentesis with albumin infusion is practiced. This increases the survival and quality of life, which improves further with placement of TIPS and after liver transplantation.

Large volume parancentesis(4-6 litres) and total volume parancentesis are equally effective. But patient with volume greater than 10 litres should have the parancentesis performed with atleast 2 weeks interim period.

Approximately 20% of large volume parancentesis are associated with post parancentesis circulatory dysfunction when not followed by volume expansion. Circulatory dysfunction involve the worsening of hyponatremia and hypovolemia which triggers the RAAS& SAS increasing the risk of renal failure, worsening of hyponatremia and decreasing survival.

Many artificial plasma expanders have been developed to substitute for albumin infusion including dextran, collagen based colloids, hydroxyethyl starches. But to date albumin remains the first choice of volume expander.

Though coagulopathy(INR>2) and thrombocytopenia (platelet count <40 thousand) are not an absolute contraindication for parancentesis, some researchers suggest correction of these parameters to avoid potential complication of abdominal wall hematoma and hemoperitoneum.

Trans jugular intrahepatic portosystemic shunt(TIPS): This procedure decreases portosystemic pressure by creating a shunt between hepatic vein and portal vein, relieving intra abdominal pressure and improving renal function. Consequently RAAS activity decreases, improving urinary sodium excretion.

The success rate associates withTIPS in between 75% to 90% depending upon the local expertise. TIPS patients have lower rate of associated recurrence of ascites(40%) than those undergoing large volume parancentesis(89%). A significant increase in survival rate was also demonstrated (p=0.009). TIPS is also shown to improve hydrothorax in 60-70% of patients.

Indication of TIPS: Refractory ascites requiring repeated parancentesis >3 times a month, have loculated ascites or multiple abdominal adhesions.

Contraindications of TIPS: These are portal vein thrombosis, hepatic encephalopathy, INR>2, SBP, age>60 years, LVEF<55%, CHILD-PUGH score greater than 12.

Complications of TIPS: Intra abdominal bleeding, hepatic encephalopathy(30%), heart failure, increased liver enzyme and shunt stenosis(40%).

Liver transplantation: It is the ultimate treatment for refractory ascites in patients wth advanced liver disease.It increases survival rate to 85% after ascites has been stabilized. TIPS and recurrent parancentesis are used as bridge therapy prior to liver transplantation to control ascites.

However in patients with normal hepatic function and serum sodium level, TIPS is associated with acceptable survival rate without transplantation.

Finally while managing with patient with refractory ascites physician must be aware of other condition that may be disguised by ascites and lead to refractory ascites such as hepatocellular carcinoma, TB and noncompliance to diet.

Hepato renal syndrome(HRS): Approximately 10% of patients with advanced cirrhosis will present with HRS. The development of HRS drastically increases the mortality when compared with refractory ascites alone. HRS is divided into 2 types:

TYPE I HRS: It is defined as acute deterioration of the kidney with a mortality rate of 80% within 2 weeks of onset. Serum creatinine level rises to >2.5 mg/dl with the level approximately doubles from the patients base line and there will be 50% decrease of 24 hr creatinine clearance from baseline to <20 ml/min in less than 2 weeks.

HRS Type I is associated with SBP in 20% of patients with dilutional hyponatremia.

TYPE II HRS: It is the commoner HRS which causes slowly progressive mild renal insufficiency(serum creatinine>1.5 mg/dl) in patients with refractory ascites. Survival rate is upto 6 months. Type II HRS can progress to type I and then prognosis worsens.

MANAGEMENT OF HRS:

The goal of treatment is to revert splanchnic vasodilatation and renal vasoconstriction. Initially diuretic should be discontinued to prevent worsening of renal failure.

A combination of vasoconstricting agents in conjunction with albumin infusion has been shown to increase survival by reversing splanchnic vasodilatation and renal vasoconstriction. Vasocontricting agent used are vasopressin agonists(terlipressin), alpha-adrenergic agonist(midodrine or nor adrenaline), octreotide plus midodrine.

Midodrine 7.5 -12.5 mg three times a day in combination with octreotide 100-200 microgram 3 times a day or terlipressin 0.5-2 mg every 4-12 hrly for 5-15 days has been shown to decrease the serum creatinine levels to no more than 1 mg/dl and bring serum sodium to near normal by improving renal perfusion and blocking splanchnic vasodilatation. The use of terlipressin has shown significant improvement of renal function in 60-75% of patient and have increased survival.

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When albumin is used with these agents, it maintains systemic plasma volume expansion by increasing the oncotic pressure and consequently increases total blood volume. The treatment effect of this therapy is maintained after treatment cessation. The infusion rate of albumin consists of albumin 1.5 mg/kg f/b 1 mg/kg 2 days later.

TIPS has shown to improve renal function in patient with HRS but further studies are required in order to determine its long term impact on survival.

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