Management of refractory ascites in cirrhosis: Are we out of date?

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Abstract
Cirrhosis is a major cause of morbidity and mortality worldwide with liver transplants as it only possible cure. In the face of a significant organ shortage many patients die waiting. A major complication of cirrhosis is the development of portal hypertension and ascites. The management of ascites has barely evolved over the last hundred years and includes only a few milestones in our treatment approach, but has overall significantly improved patient morbidity and survival. Our mainstay to ascites management includes changes in diet, diuretics, shunt procedures, and large volume paracentesis. The understanding of the pathophysiology of cirrhosis and portal hypertension has significantly improved in the last couple of decades but the changes in ascites management have not seemed to mirror this newer knowledge. We herein review the history of ascites management and discuss some its current limitations.

Key words: Portal hypertension; Cirrhosis; Ascites; Transhepatic portosystemic shunts; Paracentesis
INTRODUCTION

Ascites is the most common complication of liver cirrhosis, affecting over half of all cirrhotic patients within ten years of their cirrhosis diagnosis. The onset of ascites marks a critical point in the progression of liver disease, indicating a 50% mortality rate within 2-5 years[1]. Ascites is typically well managed with strict adherence to a low sodium diet and diuretic therapy[2]. However, in 10% of cirrhotic patients with ascites, maximal diuretic therapy is not effective[3]. In these patients with refractory tense ascites, repeated large-volume paracentesis (LVP) becomes the mainstay of chronic management.

LVP for treatment of refractory ascites is fast and effective. However, the removal of large fluid volumes may result in impaired circulatory function up to 6 d after paracentesis[4]. This complication, termed paracentesis induced circulatory dysfunction (PICD), is associated with a disruption in the renin-angiotensin axis and results in a hyperdynamic state[4]. Defined as an increase in the plasma renin activity by more than 50% of the pre-treatment value to a level of > 4 ng/mL per hour on the 6th day after paracentesis, PICD is clinically silent and not spontaneously reversible[5]. The occurrence of PICD is associated with a rapid recurrence of ascites, renal failure, and a significant decrease in the probability of survival.

Over the last three decades, only a few prospective studies with limited sample sizes and several large retrospective studies have examined PICD. Therefore, there continues to be a lack of understanding of PICD pathophysiology and management. The purpose of this review is to highlight the evidence supporting current guidelines for the management of patients with refractory tense ascites requiring repeated paracentesis.

HISTORY OF MANAGEMENT OF TENSE REFRACTORY ASCITES IN CIRRHOTIC PATIENTS

The role of paracentesis in the management of ascites

Paracentesis was first described for the management of tense ascites in the first half of the twentieth century. In the 1950s, however, paracentesis lost favor due to data associating ascitic fluid removal with complications such as hypotension, hyponatremia, acute kidney injury, and hepatic encephalopathy (HE)[6]. Two studies, one in 1967, by Knauer et al[7] and one by Guazzi et al[8] in 1975, reexamined the value of paracentesis, showing that removing between 1 and 5 L of fluid improved cardiac output (CO). They theorized that small volume removal improved CO by decreasing intra abdominal pressure, increasing venous drainage of the lower extremities, and increasing negative thoracic pressure. Several studies have since been performed in order to understand the pathophysiology and management of refractory ascites (Table 1).

In 1985, Quintero et al[9] found that paracentesis with albumin replacement adversely affected hemodynamics, renal function, hospital readmission, and mortality when compared with diuretic therapy in patients treated for tense ascites. Later that same year, Kao et al[10] studied the effects of paracentesis on circulating blood volume and suggested that paracentesis was a safe therapy in the management of tense ascites secondary to chronic liver disease. This study provided a foundation for current paracentesis guidelines in the setting of cirrhosis in which the authors “arbitrarily selected a volume of 5 L,” claiming 5 L of fluid removal to be “large enough to adequately decompress the distended abdomen while affording the patient a reasonable length of time before re-accumulation of ascites becomes a serious problem again”. The 18 patient study with strict inclusion/exclusion criteria concluded that no untoward symptoms or findings were caused by 5 L paracentesis, specifically stating that no patients were found to have symptomatic orthostatic hypotension, hyponatremia, worsening renal function, acute renal failure, or HE relatable to paracentesis. The authors did note that all patients had pitting edema, which partially improved soon after paracentesis. They concluded that the absence of clinically significant effects from LVP in their patient cohort could partially be explained by the mobilization of peripheral edema replenishing the plasma volume as it rapidly equilibrated to the loss of ascetic fluid. Thus, the authors did not recommend that their findings be applied to patients without peripheral edema.

In 1987, Salerno et al[11] investigated the role of paracentesis as a therapy for ascites when compared with traditional diuretic therapy. The study included 41 patients randomized into 2 groups who either received LVP and intravenous (IV) albumin infusions of 20-60 g after each paracentesis or were treated with diuretics and did not receive paracentesis. Salerno concluded that LVP can be performed safely and successfully with equivalent outcomes to diuretics alone. Additionally, Salerno et al[11] included patients without pitting edema in their study, administering albumin to replace 60%-80% of the protein lost in paracentesis. The authors also found that LVP decreased hospital length of stay without additional risk.

In 1988, Ginès et al[12] demonstrated that paracentesis followed by IV administration of albumin decreased the risks of renal impairment, hyponatremia, and mortality by preventing systemic hemodynamic alterations. Their study included 105 patients randomized into 2 groups; Group A (n = 52) underwent LVP followed by IV albumin infusion of 40 g and Group B (n = 53) underwent LVP (4-6 L/d) only. Serious complications were observed in 9 (17%) patients in Group A and 16 (30%) patients in Group B. Hyponatremia and renal impairment were significantly more frequent in Group B, affecting 11 (21%) patients in Group B compared with 1 (2%) patient in Group A. These findings indicated that,
### Table 1: Studies evaluating large-volume paracentesis with albumin infusion and diuretic therapy in hospitalized patients with cirrhosis and refractory ascites

| Ref. | Study design | Results | Conclusions/comments |
|------|--------------|---------|----------------------|
| Quintero et al.1985 | Total n: 72 | LVP with albumin had worse outcomes than diuretic therapy with adverse effects on hemodynamics, renal function, readmission, and mortality. | Diuretic therapy is better that LVP. |
| Kao et al.1985 | Total n: 38 underwent LVP of exactly 5 L; Exclusion criteria: Cardiac disease, chronic renal disease, active intestinal bleed, encephalopathy, 500 mg/d Na and 1 L/d fluid restriction, Diuretic discontinued 3 d prior | No untoward effects LVP of 5 L. No symptomatic hypotension or hyponatremia. No encephalopathy. Improved pitting edema. | LVP is safe in patients with peripheral edema due to mobilization of fluid to intravascular space. |
| Salerno et al.1987 | Total n: 41 patients randomized into 2 groups; Group A: Paracentesis + IV albumin: 20 patients; Group B: Paracentesis + diuretics: 21 patients; Exclusion criteria: Urinary sodium excretion rate > 20 mEq/d on a sodium-restricted diet and without diuretics; Presence of cancer, encephalopathy, active gastrointestinal bleeding, renal failure, diabetes, infection, or primary cardiac disorders; Hemoglobin < 9 g/dL; Total bilirubin > 6 mg/dL; Aminotransferases > 200 U/L; Serum urea > 60 mg/dL; Serum creatinine > 1.5 mg/dL. | Deaths: Group A: 2/20; Group B: 3/21. Complications (encephalopathy, renal failure, and gastrointestinal bleeding): Group A: 3/20 patients; Group B: 4/21 patients. | LVP is faster and equally effective alternative to diuretic therapy and suggested that LVP might be used to decrease hospital length of stay without additional risk. |
| Ginès et al.1988 | 105 patients randomized into 2 groups; Group A: Paracentesis + IV albumin: 52 patients; Group B: paracentesis without fluid replacement: 53 patients; Exclusion criteria: Similar to study by Salerno1987. | Died in hospital: Group A: 2/52; Group B: 2/53. Deaths at 1 yr: Group A: 20/52; Group B: 16/53. | These findings indicated that, aside from systemic hemodynamics, there are likely multiple factors, such as renal production of vasodilators or ADH antagonists, which contribute to the development of renal failure. |

Compliances of hyponatremia, renal impairment, encephalopathy, gastrointestinal hemorrhage, and severe infection: Group A 9/52; Group B 16/53. Group A: Significant increase in serum albumin, GFR, free water clearance. Group B: No change in serum albumin, significant increase in BUN, PRA, PAC, significant decrease in serum sodium. PRA significant increase at 48 h and 5 d post LVP. Group B 23/24 and 9/24 respectively. Group A had none. Readmission: Group A 29/52; Group B 36/53. Renal impairment: Group A: None; Group B: 11/53. |
Ginés et al. (1996) 289 patients randomized into 3 groups
Group A: Paracentesis + IV albumin: 97 patients
Group B: Paracentesis + Dextran 70: 93 patients
Group C: Paracentesis + Polygeline: 99 patients
Exclusion criteria: Similar to study by Salerno (1992)

Deaths:
Group A 2/97
Group B 4/93
Group C 6/99

PICD (based on 280 patients who developed dyspnea and had PRA measured at baseline and 6 d after the procedure):
Total 85/289
Group A 17/892
Group B 31/90
Group C 37/98
PRA > 50% increase (at 2 d after LVP) if PICD occurred: 47/85
PICD associated with shorter survival
Complications of hyponatremia, renal impairment, hepatic encephalopathy, gastrointestinal bleeding, bacterial infection
Group A: 28/97 patients, 30 complications
Group B: 28/93 patients, 43 complications
Group C: 30/99 patients, 39 complications
Incidence of death with PICD: 5/85
Incidence of death without PICD: 6/195

PICD found to not be spontaneously reversible and persists during follow-up
PICD associated with faster reaccumulation of ascites and impaired prognosis

The authors suggest that albumin is more effective than dextran 70 or polygeline at preventing postparacentesis circulatory dysfunction and is the volume expander of choice for cirrhotics who undergo paracentesis with > 5 L of ascites removed.

The authors discussed the pathophysiology of PICD, theorizing that PICD was most likely secondary to variable changes in neurohormonal responses, which accelerate the disease and lead to decreased long-term survival. They felt that PICD was unlikely due to a more advanced disease state, as patients with and without PICD did not differ in their degree of liver, renal, or hemodynamic function after paracentesis.

LVP: Large-volume paracentesis; IV: Intravenous; PICD: Paracentesis induced circulatory dysfunction; ADH: Antidiuretic hormone.

Aside from systemic hemodynamics, there are likely multiple factors, such as renal production of vasodilators or antidiuretic hormone (ADH) antagonists, which contribute to the development of renal failure.

In 1988, Pinto et al. (13) and Gentile et al. (14) both independently studied the hemodynamic and hormonal impacts of LVP of exactly 5 L in 12 non-edematous cirrhotic patients. Both studies concluded that LVP of 5 L could be safely performed without significant changes in plasma volumes, PRA, or vasopressin. They did, however, note a significant decrease in diastolic pressure and a significant increase in aldosterone, which corresponded with reduced urinary sodium excretion.

In 1990, Panos et al. (15) confirmed an earlier finding of Simon et al. (16) in 1987 that, up to 3 h after LVP, CO increased, right atrial pressure decreased, and pulmonary capillary wedge pressure (PCWP) remained the same. After 3 h post-LVP, right atrial pressure, PCWP, and CO all decreased significantly. These findings indicated that, although paracentesis initially results in hemodynamic improvement, a relative hypovolemia occurs hours after paracentesis.

Two studies in 1990 and two in 1991 evaluated the effect of various IV infusions to prevent hypovolemia after LVP (17). The studies included comparisons between albumin, dextran-70, dextran-40, hemaccel, and saline (18). They concluded that dextran-70, albumin, and hemaccel were all equally effective in preventing renal and electrolyte complications, while dextran-40 was ineffective. A third study by Cabrera et al. (19) in 1990 found that IV saline prevented hypovolemia with no changes in PRA or aldosterone.

Albumin was effective in preventing hypovolemic complications, however, it was a costly product. To investigate possible alternatives, Planas et al. (18) conducted a randomized trial comparing the efficacy of three different plasma expanders for preventing, PICD. PICD was defined as an increase in PRA of more than 50% of the pretreatment value to a level of > 4 ng/mL per hour on the 6th day after paracentesis. This pretreatment value was determined by the upper value of PRA found in 36 healthy subjects studied on a 50-mmol/d sodium diet and was arbitrarily chosen to represent physiologically relevant activation of the renin-angiotensin system. In the study of Planas et al. (18), patients were randomized to receive one of the three infusion types: Albumin, dextran-70, or polygeline. Eighty-five patients developed PICD, with a significantly greater frequency when treated with dextran-70 (34.4%) and polygeline (37.8%) than when treated with albumin (18.5%). Additionally, they found a significantly higher 6-mo mortality rate in patients who develop PICD. They further concluded that PICD was predictive in fluid removal > 5 L with the use of dextran-70 or polygeline. This trend did not appear in patients receiving > 5 L of fluid removal followed by albumin infusion. The authors discussed the pathophysiology of PICD, theorizing that PICD was most likely secondary to variable changes in neurohormonal responses, which accelerate the disease and lead to decreased long-term survival. They felt that PICD was unlikely due to a more advanced disease state, as patients with and without PICD did not differ in their degree of liver, renal, or hemodynamic function after paracentesis.

The following year, in 1997, Ruiz-del-Arbel et al. (20) demonstrated an inverse correlation between PRA and systemic vascular resistance (SVR) associated with PICD. Out of the 37 patients who underwent LVP (mean > 7 L) followed by a dextran-70 infusion, 10 (27%) developed PICD. More specifically, they found that despite the normalization of PRA, aldosterone, and norepinephrine...
by the 6th day after paracentesis, cardiopulmonary pressures and SVR remained lower than baseline. The authors believed that LVP is an inciting event that leads to an accentuation of the vasodilatory response already present in cirrhotic patients. This exaggerated vasodilatory response then causes an increase in PRA to compensate for increases in SVR. In addition, utilizing a transjugular intrahepatic venous catheter they found that the hepatic venous pressure gradient did not change in patients without PICD but increased significantly, secondary to PRA, if PICD occurred. They theorized that this was also likely due to endogenous vasoactivation.

In 1998, Vila et al.21 confirmed these conclusions and also found that if effective hypovolemia did not develop, there were no significant changes in CO, CVP, or SVR and there was a significant reduction in PRA at the 1 and 3 h period after paracentesis. In contrast, if effective hypovolemia did develop, there were significant reductions in CO, CVP and SVR, no change in PRA or aldosterone level, and an increase in CO. This paradoxical finding was believed to be due to physiological responses secondary to abrupt falls in intraabdominal pressure after paracentesis procedures.

In a pilot study in 2002, Moreau et al.22 compared the effect of terlipressin and albumin on arterial blood volume in 20 cirrhotic patients who underwent paracentesis. Assuming that PICD is predominantly caused by exacerbation of an already dilated arterial system, the authors theorized that terlipressin, a vasoconstrictor, may prevent PICD more effectively than albumin. After paracentesis, 10 patients received albumin and the other 10 received terlipressin. They found that both treatments had the same beneficial effect of preventing arterial vasodilation. The authors favored the use of terlipressin, arguing for cheaper cost.

In 2003, Sola-Vera et al.23 compared PICD in 37 patients receiving albumin and 35 patients receiving saline infusion after LVP. They found that patients who received saline had a significant increase in PRA and PAC on the 6th day after paracentesis, which contradicted data published by Cabrera et al.19 in 1990. Only 11% of patients developed PICD after albumin infusion compared to 33% after saline infusion. If < 6 L was removed, the PICD was similarly low in both groups (6.7% in albumin group vs 5.6% in saline group). Additionally, they found that nitric oxide (NO) was elevated in the saline group and likely contributed to the pathogenesis of PICD.

The prevention of PICD using albumin infusion was compared to the use of midodrine post-paracentesis in a study by Appenrodt et al.24 in 2008. They performed a blinded study in 24 patients with tense ascites and included patients with similar comorbidities as prior studies. Additionally, since this study was conducted after the inception of MELD scoring in 2002, they reported a mean MELD of 11 in both the midodrine and albumin groups. Midodrine was given immediately after paracentesis at a dose of 12.5 mg orally every 8 h for 2 d. In the midodrine group, they found a large, but insignificant, increase in the PRA level on day 6 after paracentesis. They concluded that the used of midodrine was less effective than albumin in preventing PICD.

In 2010, Nasr et al.25 evaluated the risk factors for PICD. The study included 45 patients with cirrhosis and used similar inclusion criteria as the prior studies mentioned. The patients received either albumin or dextran-70 post-paracentesis and the volume removed ranged from 8 to 18 L. They evaluated several demographic, clinical and laboratory factors, and found, based upon logistic regression analysis, that only the use of dextran-70 and younger age were independent predictors of PICD.

A multicenter trial including 26 patients was published in 2011 by Fimiani et al.26. This trial evaluated the impact of a combination of diuretics, albumin, and terlipressin in treating tense ascites. The study examined several clinical factors after paracentesis, including ascites recurrence, body weight, abdominal circumference, and urinary sodium excretion. The combination of changes in these factors was given a grade of severity and a degree of response. Based upon these definitions, they concluded that combination treatment decreased the need for repeated LVP, improved urinary sodium, reduced abdominal circumference, and decreased the severity of ascites.

In the same year, Alessandria et al.27 compared the efficacy of different volumes of post-paracentesis albumin infusion, comparing the incidence of PICD between patients who received 4 g of albumin per liter of fluid removed and patients who received 8 g of albumin per liter of fluid removed. They found the same incidence of PICD, hyponatermia, and renal failure in both groups and concluded that half the standard dose of albumin is as effective and safe as the full standard dose in patients undergoing paracentesis.

In 2013, Carl et al.28 performed a small trial including 10 patients with the purpose of studying the relationship between inflammation and PICD after LVP. They looked at several factors over a 24-h period, including blood pressure, BUN, creatinine (Cr), PRA, aldosterone, angiotensin II, asymmetrical dimethylarginine (ADMA), norepinephrine, CD14, interleukin-6, tumor necrosis factor-alpha, and monocyte chemotactic protein-1 (MCP-1). Both MCP-1 and CD14 increased concurrently while blood pressure decreased in the 24 h after LVP. These results suggested that the inflammatory cascade may be involved in the genesis and severity of PICD.

The role of transhepatic portosystemic shunts in the management of ascites

Until 1996, large volume paracentesis was the standard therapy for refractory tense ascites. Although this was proven to be an effective treatment approach, it did not address the underlying issue of portal hypertension. After LVP, ascites would quickly re-accumulate and require repeated paracentesis. On the other hand, a transhepatic portosystemic shunts (TIPS) has the potential to mitigate portal hypertension by diverting portal blood flow from the liver directly into the systemic

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venous circulation via an intrahepatic shunt. Several studies have been conducted comparing TIPS to LVP\textsuperscript{29} (Table 2).

In 1996, Lebrec \textit{et al}\textsuperscript{30} compared the effect of TIPS and LVP in 25 cirrhotic patients with refractory ascites who were randomized to TIPS or repeat LVP. The authors concluded that intrahepatic shunts were selectively effective in patients with Childs-Pugh class B, although they did not improve survival, and actually decreased survival in class C patients compared to LVP. They believed that the prominent factor is ascites management were dependent on both neurohormonal factors which control natriuresis and the hepatic sinusoidal pressures.

In 2000, Rössle \textit{et al}\textsuperscript{31} conducted a similar randomized study in 60 patients comparing TIPS to LVP. Fifteen of the 29 TIPS patients died while 23 of the 31 LVP patients died at 1 year. Although 10 patients required rescue shunt treatment, no deaths or long-term illnesses occurred secondary to the shunting procedure. In comparison with LVP, the creation of a transjugular intrahepatic portosystemic shunt can improve the chance of survival without liver transplantation in patients with refractory or recurrent ascites.

In 2002, Ginès \textit{et al}\textsuperscript{32} published a study comparing survival rates and associated healthcare costs between patients receiving TIPS and patients receiving paracentesis with albumin replacement. Seventy cirrhotic patients with refractory ascites were selected for the study and randomly assigned to either undergo TIPS (n = 35) or repeat LVP (n = 35) with albumin infusions. MELD scores were not used, as this was conducted prior to the start of MELD scoring. They concluded that TIPS lowers the rate of ascites recurrence and the risk of developing hepatorenal syndrome, but does not improve survival and has increased occurrence of encephalopathy and higher cost than LVP.

In 2003, Sanyal \textit{et al}\textsuperscript{33} also compared TIPS to LVP in 109 patients with refractory ascites. The LVP group consisted of 57 patients who received low sodium diets, diuretics, and LVP. The TIPS group consisted of 52 patients who received TIPS in addition to the same low sodium diets and diuretics as the LVP group. In the first year following randomization, they found that 22 (42%) TIPS patients and 48 (84%) LVP patients required repeat LVP’s for recurrent tense ascites. The average rate of paracentesis per patient in the first year was 1.69 for TIPS patients and 6.11 per year for LVP patients. Mortality was 21 (40%) in the TIPS group and 21 (37%) in the LVP group. Sixteen (31%) TIPS patients and 17 (30%) LVP patients received liver transplants.

In 2004, Salerno \textit{et al}\textsuperscript{34} randomized 65 cirrhotic patients with refractory ascites into 2 groups. Thirty-two patients received TIPS and 33 patients received LVP. Mean baseline MELD was 11.1 ± 0.8 in the TIPS group and 11.1 ± 0.9 in the LVP group. The Cox proportional hazard model indicated that the treatment assigned and MELD scores were independent predictors of mortality. In 2007, Salerno \textit{et al}\textsuperscript{35} published a meta-analysis based upon individual patient data on outcomes of TIPS for refractory ascites. The study included all published data from randomized control trials with available patient data. This excluded the study by Lebrec \textit{et al}\textsuperscript{30}, which was the only study to show a negative effect of TIPS on survival. Salerno \textit{et al}\textsuperscript{35} concluded: (1) TIPS improves transplant-free survival compared to LVP; (2) patient survival is independently associated with age, bilirubin levels, and serum sodium concentrations; (3) the risk of ascites recurrence is decreased with TIPS; (4) the probability of HE after TIPS is increased; and (5) patients with low arterial pressure, high MELD score, and low portosystemic pressure gradient after TIPS have the greatest probability of experiencing post-TIPS HE.

**PATHOPHYSIOLOGY OF PICD**

Over the last three decades, LVP has become more widely accepted as the standard first line approach in treating refractory tense ascites, we have gained further insight into the pathophysiology of PICD. Portal hypertension is a major sequel of cirrhosis and occurs secondary to increases in intrahepatic resistance to portal blood flow\textsuperscript{36}. The deposition of collagen in the hepatic acinus of the cirrhotic patient leads to narrowing of the sinusoidal lumen, compression of the venules due to regenerative nodules, the development of fibrosis, and portal inflammation\textsuperscript{11}. Each of these sequelae contribute to liver stiffness, which resists the inflow of portal blood\textsuperscript{37}. In addition to these structural changes, there are several neuro-hormonal factors that alter the contractile tone of intrahepatic endothelial cells\textsuperscript{38}. Shear stress and bacterial translocation occurs, leading to endothelial dysfunction in the pre-sinusoidal areas. This causes the release of NO and the increased production of COX-derived prostanooids\textsuperscript{39}. The combination of portal blood flow resistance due to cirrhosis and increased arterial inflow from splanchnic vasodilation leads to portal hypertension. Portal hypertension is maintained by the opening of portal-systemic collaterals as well as the generation of new vessels via angiogenesis. Splanchnic vasodilation is mediated by several substances, including glucagon, prostacyclin, intestinal vasoactive peptide, histamine, substance P, estrogens, cholecystokinin, ammonia, endotoxins, adenosine, biliary acids, NO, alphacalcitonin gene-related peptide, vascular endothelial growth factor, adenomedullin, carbon monoxide, and endogenous cannabinoids\textsuperscript{39}.

There is a complex and relatively poorly understood interaction between these mediators in controlling blood flow. Recently, it has been suggested that NO plays a prominent role. However, several \textit{in vitro} studies have demonstrated variable changes in compensatory factors when NO is inhibited or promoted, suggesting that its control is not the only important factor. In response to the release of vasodilators in the splanchnic system, there is a release of vasoconstrictors. Due to the high levels of NO and CO, these vasoconstrictors have a blunted effect on splanchnic circulation and mostly affect the kidneys.
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### Table 2: Randomized control studies evaluating transhepatic portosystemic shunts vs paracentesis in patients with cirrhosis and refractory ascites

| Ref. | Study design | Results | Conclusions/comments |
|------|--------------|---------|---------------------|
| Lebrec et al[30], 1996 | Total of 25 13 TIPS 12 LVP Excluded: Age > 70 Severe diseases other than liver Pulmonary hypertension Hepatocellular carcinoma Hepatic encephalopathy Sepsis/spontaneous bacterial peritonitis Severe alcoholic hepatitis Portal/hepatic vein obstruction/thrombosis Obstruction of biliary tract or hepatic artery Plasma creatinine > 150 mmol/L | Deaths: TIPS - 9/13 LVP - 4/12 3/13 TIPS unsuccessful, of the remaining 10/13 TIPS patients 8 required a second shunt and 2 required 3 shunts 1/12 LVP patients received liver transplant Survival at 2 yr with 'intention to treat' analysis 29% ± 13% for TIPS and 60% ± 16% for LVP | The authors concluded that intrahepatic shunts were selectively effective in patients with Child-Pugh class B, although they did not improve survival, and actually decreased survival in class C patients compared to LVP. They believed that the prominent factor is ascites management were dependent on both neurohormonal factors which control natriuresis and the hepatic sinusoidal pressures |
| Rössle et al[31], 2000 | Total of 60 patients Randomized to 2 groups: TIPS 29/60 LVP 31/60 Excluded: Hepatic encephalopathy > Grade 2 Serum bilirubin > 5 mg/dL Serum creatinine > 3 mg/dL Portal-vein thrombosis Hepatic hydrothorax Advanced cancer Continual ascites after paracentesis or multiple paracentesis within 1 wk | Deaths: TIPS - 15/29 LVP - 23/31 13/29 patients had shunt insufficiency, 11/29 underwent reestablishment of the shunt after 10 ± 16 mo and 5 of these patients required a second reestablishment 1/29 TIPS patients received liver transplant Survival at 2 yr with 'per protocol' analysis was 38% ± 16% for TIPS and 70% ± 15% for LVP | In comparison with large-volume paracentesis, the creation of a transjugular intrahepatic portosystemic shunt can improve the chance of survival without liver transplantation in patients with refractory or recurrent ascites |
| Ginès et al[32], 2002 | Total of 70 patients randomized into 2 groups TIPS: 35 LVP + Albumin (8 g/L ascites removed): 35 Primary endpoint: Survival without liver transplantation Secondary endpoints: Complications of cirrhosis and cost Excluded: < 18/> 75 years old Serum bilirubin > 10 mg/dL Prothrombin time < 40% Platelet count < 40000/mm³ Serum creatinine > 3 mg/dL Hepatocellular carcinoma Complete portal vein thrombosis Cardiac/respiratory failure Organic renal failure Bacterial infection Hormonal measurements (plasma renin) | Deaths: TIPS 20/35 LVP 18/35 Transplanted: TIPS 7/35 LVP 7/35 1 TIPS patient required repeat LVP’s 3 LVP patients required TIPS placement | They concluded that TIPS lowers the rate of ascites recurrence and the risk of developing hepatorenal syndrome, but does not improve survival and has increased occurrence of encephalopathy and higher cost that LVP |
Splanchnic vasodilation leads to an abnormally increased distribution of blood into the mesenteric circulation. Over time, there is an exaggerated disequilibrium of blood supply between the central and non-central volumes, characterized by a decrease in the central (heart, lungs, and brain) blood volume and an increase in the non-central (splanchnic) blood volume. These shifts in blood volume are not clinically significant in the early stages of cirrhosis but become more relevant as the disease worsens. With the development of non-central vasodilation and pooling of blood in the mesenteric circulation, there is an initial compensatory increase in CO and a decrease in MAP and SVR. With the activation of baroreceptors, this is accentuated over time, causing further increases in CO and heart rate. As the sympathetic nervous system, renin-angiotensin-aldosterone system, arginine-vasopressin, and endothelin responses heighten, renal vascular resistance increases. This increase causes vasoconstriction and decreased activity, aldosterone, norepinephrine, and atrial natriuretic peptide were measured at 1 wk, 1 mo and 6 mo in 18 TIPS patients and 23 LVP patients. Total costs for TIPS patients (calculated separately in United States dollars on intention-to-treat basis from Spanish and then United States hospitals that participated in the study) demonstrated that total costs and costs per patient were greater in the TIPS group TIPS $693460, or $19813 per patient. LVP patients were $341760, or $9765 per patient. Although TIPS plus medical therapy is superior to medical therapy alone for the control of ascites, it does not improve survival, affect hospitalization rates, or improve quality of life. Sanyal et al(33), 2003 109 patients with refractory ascites were randomized into 2 groups 52 patients received TIPS with medical therapy (low sodium diets, diuretics, and LVP) 57 patients received medical therapy without TIPS Excluded: Similar criteria to prior studies All patients placed on low Na diets and diuretics All patients placed on low Na diets and diuretics Diuretics stopped 5 d prior to LVP Albumin infusion followed LVP at 6-8 g/L removed TIPS patients received shunts Some patients from both groups received repeat LVP’s plus Albumin for tense, symptomatic ascites with weight gain > 10 pounds Deaths: TIPS - 21/52 LVP 21/57 Failed Treatments: TIPS 3/52 unsuccessful LVP 2/57 patients required TIPS Failed treatments in the first year after randomization requiring repeat LVP for tense ascites: TIPS - 22/52 LVP 46/57 Average rate of LVP per patient in the first year after randomization: for TIPS - 1.69 LVP - 6.11 Transplants: TIPS 16/52 LVP 17/57 Salerno et al(34), 2004 66 patients randomized into 2 groups TIPS group: 33 LVP + Albumin group: 33 Excluded: Similar criteria to prior studies Diuretic doses continued throughout the study and doses adjusted for each patient’s clinical needs All patients on low Na diets (80 mg/d) TIPS placed LVP patients received Albumin replacements at 8 g/L ascites removed Patients discharged and followed at 1, 3 and 6 mo, then every 3-6 mo or as clinically necessary Mean follow up time was 18.2 ± 2.3 mo Deaths: TIPS - 13/33 LVP - 20/33 Failed treatments: TIPS - 3/33 Initial LVP - 0/33 reported Estimated probability of survival at 1 yr: TIPS - 77% LVP - 52% Estimated probability of survival at 2 yr: TIPS 59% LVP 29% Transplanted: TIPS 4/33 LVP 4/33 Failure of treatment noted in 7/33 TIPS patients: 2 patients received LeVeen Shunts and 5 LVP’s Failure of treatment noted in 19/33 LVP patients: 1 received a LeVeen Shunt, 11 elected to continue with LVP treatment Cox proportional hazard model indicated that treatment assigned and MELD scores were independent predictors of mortality. Failure of treatment noted in 7/33 TIPS patients: 2 patients received LeVeen Shunts and 5 LVP’s. Compared to large-volume paracentesis plus albumin, TIPS improves survival without liver transplantation in patients with refractory ascites. LVP: Large-volume paracentesis; TIPS: Transhepatic portosystemic shunts; MELD: Model for end-stage liver disease.
renal blood flow leading to sodium and water retention. Over time, as more blood volume sequestration occurs in the splanchnic system, the compensatory mechanisms are unable to sustain blood flow, leading to tissue hypoxemia and end-organ damage. This cascade of pathophysiological responses to portal hypertension is termed hyperdynamic circulatory syndrome and is generally characterized by an increase in CO and heart rate and a decrease in SVR and MAP[36].

Most patients who require LVP to manage refractory ascites exhibit hyperdynamic physiology, with increased CO and heart rate and decreased MAP. Generally after paracentesis, there is an immediate and significant decrease in intraabdominal pressure. This leads to initial hemodynamic improvement, increasing CO as venous return and negative thoracic pressures improve. In general if less than 5 L of fluid is removed, there appears to be no ill effects of paracentesis. If > 5 L, or an “LVP”, is performed, relative hypovolemia develops hours after the procedure[40]. This causes a series of complex neurohormonal responses that are not well understood. It appears that within 1 h after LVP, there is an increase in cardiac index and an associated decrease in SVR. There are discrepant findings in the literature regarding the pathophysiological cause of the decrease in SVR. However, it may be related to improved CO alone or changes in both the renin-angiotensin system and the sympathetic nervous system. The exact neurohormonal changes, sequence of events, progression over time, and impact on the cardiovascular and renal systems are also not clear. Overall, the initial improvement in hemodynamics after paracentesis is followed by a relative hypovolemia. This leads to circulatory dysfunction demonstrated by increased PRA, ADH, and aldosterone levels and decreased MAP and SVR. This constellation of events, termed PICD, is most commonly associated with hyponatremia and renal insufficiency[5].

SUMMARY AND CURRENT CLINICAL PRACTICE GUIDELINES ON MANAGEMENT OF REFRACTORY ASCITES

Refractory ascites is defined as fluid overload that is unresponsive to high-dose diuretics (spironolactone 400 mg/d and furosemide 160 mg/d) and sodium-restrictive diets, recurring rapidly after therapeutic paracentesis[36]. Diuretic therapy is considered to have failed when there is minimal or no weight loss coupled with poor urinary sodium restriction (< 78 mmol/d) or when there are clinical complications of encephalopathy, serum Cr > 2.0 mg/dL, serum sodium < 120 mmol/L, or serum potassium > 6.0 mmol/L. Initial failure of diuretic therapy should be treated medically (fluid restriction, sodium restriction, and diuretic therapy), followed by serial LVP while awaiting liver transplant. If LVP is not feasible, TIPS or surgical peritoneovenous shunting is recommended[1,41].

The American Association for the Study of Liver Disease (AASLD), the European Association for the Study of Liver Disease, and International Ascites Club have written review articles and recommended summary guidelines for the management of ascites secondary to portal hypertension in cirrhotic patients. The most recent AASLD practice guideline update, published in 2012 by Runyon, made several recommendations for treating cirrhotic patients diagnosed with refractory ascites. The guidelines stated that: (1) beta blockers should be discontinued or not initiated due to risks of complications of systemic hypotension and evidence of decreased survival (Class III, Level B); (2) angiotensin converting enzyme inhibitors should be avoided due to complications of hypotension (Class III, Level B); (3) in patients with hypotension, randomized trials have shown that oral midodrine (7.5 mg TID) improves urinary volume, urine sodium, MAP, and survival theoretically due to its ability to improve blood pressure and convert patients from diuretic-resistant to diuretic-sensitive (Class Ia, Level B); (4) after discontinuation of beta blockers and administration of midodrine, refractory ascites should be treated with serial LVP (Class I, Level C); (5) following a single paracentesis of < 4-5 L, albumin infusion may not be required to prevent PICD (Class I, Level C); (6) LVP (> 5 L), requires albumin infusion of 6-8 g/L of fluid removed to improve survival (Class IIa, Level A); (7) TIPS should be considered in patients who meet criteria as described in above mentioned randomized trials but is considered a second line therapy after LVP (Class Ia, Level A); and (8) peritoneovenous shunting should be performed if patients are not candidates for paracentesis, TIPS, or transplant (Class IIb, Level A). These are the current management guidelines to which most transplant centers in North America adhere.

ISSUES AND CONTROVERSIES

In our review of the literature regarding the management of refractory ascites, there are several major issues. The first liver transplant was performed in 1963 but it did not become a practical therapy for patients with end-stage liver disease until the 1980’s when the use of cyclosporine for preventing organ rejection allowed long-term patient survival. Research efforts in cirrhosis have since intensifed, but the pathophysiology of the complications of cirrhosis remain incompletely understood. As such, research has tended to compartmentalized each of the various complications. While many complex diseases are evaluated using this method of scientific research, cirrhosis may require a more holistic approach since cirrhosis occurs affects essentially every organ system in the body during its progression.

Our current understanding of ascites and its management seems to be based, in large measure, on evidence and observations derived from research performed decades ago. Furthermore, the evidence is based on a focused perspective rather than a global one and does not take into account the dynamic and evolving
systemic nature of cirrhosis.

Large volume paracentesis is defined as a volume of > 5 L. This amount of fluid removal is somewhat arbitrary, originally coined in 1987 by Kao et al.\(^1\) based upon a description of the volume required to "flatten the abdomen". Since then, LVP of > 5 L has been used universally as the gold standard when considering fluid replacement. We could not find a single study that examined the impact of variations in paracentesis volume on neuro-hormonal changes in equivalent patients. Hence, we would challenge the validity of defining a 5 L paracentesis as what constitutes a "large volume".

In addition, a paracentesis volume of > 5 L is considered the amount above which PICD occurs. Before 1986, there were few studies that analyzed patients with paracentesis of < 5 L. In the studies published since 1986, which evaluate the impact of fluid replacement, neuro-hormonal responses, and effects of medications on PICD, the mean volumes of paracentesis were always > 5 L. Thus, it is unclear how the conclusion that a paracentesis of > 5 L causes PICD can be made when no significantly sized group of similar patients with < 5 L fluid removal have been compared. It is likely that the occurrence of physiologically significant changes after paracentesis are dependent upon a multitude of factors and not only on this "minimum" amount of 5 L of removal.

Patient volume status, fluid responses, medication doses, and many other physiological effects are based upon patient sex, height, weight, muscle mass, renal function, or body mass index (BMI). Along the same lines, one would assume that the effect, responses, and management of fluid shifts in cirrhotic patients undergoing paracentesis should be affected similarly. The accepted management guidelines for refractory ascites requiring paracentesis does not incorporate any of these principles and is instead based only on a removal volume of > 5 L. Although never studied, it is more likely that physiological responses after paracentesis in cirrhotic patients have a graded effect based upon variables such as milliliter of fluid removed per kilogram body weight, BMI, muscle mass, and sex.

Additionally, the definition of PICD as "an increase in the plasma renin activity by more than 50% of the pretreatment value to a level of > 4 ng/mL per hour on the 6th day after paracentesis" appears to have been arbitrarily created based upon the mean PRA levels of 36 healthy subjects. Studies conducted based upon this definition showed that PICD is associated with decreased 6-mo survival. It can be safely concluded that there is survival disadvantage when untoward effects of paracentesis occur, but it is not exactly clear what the "cut-off" values of PRA should be. Another approach may be to linearly determine the effect of changes in PRA on mortality and hence determine what correctly defines LVP. Because PICD has been associated with hyponatremia and renal insufficiency, there may be some utility in proving end organ damage. However, it is not clear how this can be achieved in cirrhotic patients who already have significant multi-organ compromise. One crude method would be to assess mixed venous oxygenation or lactate levels at different time points after paracentesis.

Our current management guidelines for refractory ascites and PICD are based upon physiological effects of LVP determined in studies conducted before the inception of MELD scoring in 2002. Although individual patient data is not available, based upon the patient characteristics published in each manuscript, the mean MELD scores of the groups of patients included in these studies appears to be < 15. In our current era, the mean MELD at the time of transplant ranges from 23-35 depending on the UNOS Region. Given this difference in disease severity, the effects of paracentesis established in previous studies may not be applicable in patients with more advanced cirrhosis. There is no published data comparing the effects of similar volumes of paracentesis with more progressive cirrhosis or higher MELD scores.

Furthermore, all of these studies had very strict inclusion criteria, excluding patients with common cirrhosis complications, such as HE, active gastrointestinal bleeding, renal failure, diabetes, infection, cardiac disorders, hemoglobin < 9 g/dL; total bilirubin lower than 6-10 mg/dL; and serum creatinine < 1.5-3 mg/dL, or platelet count > 40000. As cirrhosis progresses, most patients develop these complications and begin to exhibit hyperdynamic physiology. These patients often have refractory ascites and require more frequent paracentesis. However, the exact same paracentesis guidelines are applied in these patients with decompensated cirrhosis as in patients with a MELD < 15. It is likely that patients with advanced cirrhosis lack the pathophysiological reserve to compensate for paracentesis-induced fluid shifts. It is therefore imperative that we continue to examine the evolving hemodynamic and neurohormonal responses in this sicker group of patients and adjust the way we manage paracentesis and PICD.

**CONCLUSION**

Paracentesis is a mainstay for the treatment of refractory ascites in patients with cirrhosis. There is clear evidence that there is a decrease in survival in patients who undergo paracentesis and develop circulatory dysfunction. Our current guidelines for the management of patients requiring paracentesis are founded on a few studies from several decades ago, which include patients with well-compensated cirrhosis. Moreover, current guidelines are based on definitions of LVP and PICD created arbitrarily and without a significant amount of comparative evidence. Yet, we continue to apply these guidelines to all cirrhotic patients with ascites, regardless of patient demographics, co-morbidities, or degree of disease decompensation. A more accurate and discriminating understanding of the acute neuro-hormonal, hemodynamic, and end organ effects of fluid shifts and how these factors impact patients with more
decompensated cirrhosis is needed.

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