Digestive Diseases and Sciences, Vol. 42, No. 1 (January 1997), pp. 161–166

Treatment of Refractory Ascites Using Transjugular Intrahepatic Portosystemic Shunt (TIPS)

A Caution

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Ascites becomes refractory to medical treatment in nearly 10% of cirrhotic patients, who then require repeated large-volume paracentesis. In this prospective study we evaluated the use of transjugular intrahepatic portosystemic shunt (TIPS) in 30 patients with refractory ascites. TIPS was successful in all and resulted in a 54% reduction in portacaval gradient (from 22.8 ± 0.8 to 10.4 ± 0.6 mm Hg). Ascites became easily controlled with diuretics in 26 patients following TIPS. Ascites recurrence associated with shunt stenosis was observed during follow-up in eight patients; revision could be undertaken in five of them and resulted in good control of ascites. In responders, a marked decrease in plasma aldosterone and renin activity, a reduction in serum creatinine, and a rise in urinary sodium excretion were observed. Creatinine and inulin clearances improved significantly; PAH clearance remained unchanged. However, new-onset or worsening hepatic encephalopathy was seen in 14 patients. Severe disabling chronic encephalopathy occurred in five patients; it could be reversed successfully by balloon occlusion of the shunt in three. The cumulative survival rate was 41 and 34% at 1 and 2 years, respectively. In summary, TIPS can control refractory ascites in a majority of patients but is associated with a high rate of chronic disabling HE. In addition, the survival rate is poor. Randomized trials are needed to evaluate the exact role of TIPS in the management of refractory ascites. It is unlikely to improve survival but can ameliorate quality of life in nontransplant candidates and be useful as a bridge to transplantation, in particular, to improve denutrition associated with longstanding tense ascites.

KEY WORDS: refractory ascites; transjugular intrahepatic portosystemic shunt; portacaval shunt; hepatic encephalopathy.

Ascites is a common major complication of cirrhosis and is a sign of advanced liver disease. In a vast majority of patients, ascites can be controlled by dietary sodium restriction and diuretics. However, nearly 10% of patients with ascites later become resistant, either being unresponsive to medical treatment or developing complications related to large doses of diuretics (encephalopathy, hyponatremia, renal failure). Therapeutic options in this situation include repeated large volume paracentesis, continuous ultrafiltration–reinfusion of ascitic fluid, peritoneojugular (Leveen) shunt placement, surgical portacaval shunt, and liver transplantation (1). Repeated large-

Manuscript received January 10, 1996; revised manuscript received June 4, 1996; accepted September 18, 1996.

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volume paracentesis is the most widely used technique as it is a rapid, safe, and inexpensive therapy; survival in patients treated by this method is similar to that observed after Leveen shunt (2,3). The surgical portacaval shunt is extremely efficient for clearing ascites; however, it is associated with a significant operative mortality and chronic hepatic encephalopathy is a major problem during follow-up (4-5). Transjugular intrahepatic portosystemic shunt (TIPS) is an equivalent of the surgical shunt; however, this procedure is performed without laparotomy or general anesthesia. In addition, it induces only a partial diversion of portal flow in a majority of patients. Therefore, TIPS can combine the effectiveness of surgical shunting and the safety of a non-surgical approach. The aim of the present study was to evaluate the effectiveness and safety of TIPS in the treatment of refractory ascites using a prospective pilot study.

PATIENTS AND METHODS

All patients with portal hypertension and refractory ascites (admitted between March 1992 and May 1994) were considered for inclusion in the present study. Refractory ascites was defined as follows: absence of weight loss using large doses of diuretics (aldactone or triamterene, 200 mg/day, + furosemide, 80 mg/day, + metolazone, 2.5 mg/day) or appearance of diuretic-induced hepatic encephalopathy, hyponatremia (serum sodium, <125 mEq/L), or renal failure (50% increase in serum creatinine above baseline values), despite a daily dietary sodium intake of 80 mmol/day and after a 6-month period of observation.

Patients with organic renal disease as defined by proteinuria >3 g/day, the presence of urinary casts on the sediment, or a long-standing increase in serum creatinine above 200 mM were not eligible for inclusion. Patients with portal vein thrombosis, hepatocellular carcinoma, end-stage liver failure (Pugh score >12), respiratory or cardiac failure, and inability or refusal to consent were also excluded from the study.

The study group included 30 patients. The diagnosis of the liver disease was established by liver biopsy in all. The study was approved by our local ethics committee and an informed written consent was obtained from each patient.

Before the TIPS procedure, patients underwent physical examination, ECG, chest X-ray, and Doppler ultrasound of the liver and portal venous system, as well as the following biochemical tests: serum urea, creatinine, electrolytes, albumin, bilirubin, AST, ALT, alkaline phosphatase, complete blood count, prothrombin time (INR), daily urinary sodium excretion, and creatinine clearance.

A subgroup of 15 patients underwent a more detailed evaluation after a 3-day diuretic-free period including the following measurements: glomerular filtration rate (GFR) using inulin clearance and renal plasma flow using p-aminohippuric (PAH) clearance.

TIPS placement was performed as described previously using a combination of Palmaz stent (Johnson and Johnson, Warren, NJ) and Wallstent (Schneider, Minneapolis, MN). The procedure was done under sedation using fentanyl. Antibioprophylaxis consisting of cefotaxime and cloxacilline was administered before and for 24 hr following the procedure. No anticoagulation was given. During the procedure, the following pressure measurements were obtained, before and immediately after shunting: mean arterial pressure (MAP), right arterial pressure (RAP), inferior vena cava pressure (IVCP), and portal vein pressure (PVP); the portacaval gradient (PCG) was calculated as the difference between PVP and IVCP. In addition, samples were obtained from the jugular vein at the beginning of the procedure for the measurement of plasma aldosterone, renin activity, and norepinephrine.

Patients were discharged under a salt-restricted (80 mmol Na/day) and protein-restricted (60 g/day) diet. Lactulose was administered prophylactically during the first month following the procedure. Diuretics were reintroduced before discharge and adjusted according to the clinical response. Patients were followed in a specialized TIPS clinic every 2 weeks for 2 months, monthly for 3 months, and every 3 months thereafter.

An evaluation of shunt function was performed systematically every 2–3 months using duplex Doppler ultrasonography. Measurement of the portohepatic gradient was performed under antibioprophylaxis at 2 months and 1 year after stent placement. If hemodynamic evaluation, performed routinely or subsequent to Doppler examination suggesting shunt malfunction (6), disclosed a PCG greater than 12 mm Hg, an attempt was made to decrease the pressure using stent dilatation, addition of a new stent, or both.

Patients who were evaluated at baseline after a 3-day diuretic-free period had a second set of measurements 2 months after TIPS including PAH, inulin, and creatinine clearances, 24-hr urinary sodium excretion, plasma aldosterone, renin activity, and norepinephrine. Pressure measurements were obtained after shunt catheterization during the same admission.

TIPS was judged as efficient if the patient had good control of ascites (with or without diuretics) without the need for further large-volume paracentesis during follow-up.

The diagnosis of encephalopathy was based on clinical examination and classified as mild (time-limited episodes with a well identified precipitating factor), moderate (recurrent episodes easily managed by diet and/or medication), or severe (onset of episodes of encephalopathy despite chronic treatment including protein-restricted diet, lactulose, and metronidazole).

Methods of Measurements. Plasma renin activity was measured by radioimmunoassay [Rianen angiotensin I [125] RIA kit, Du Pont company, Billenda, MA]. Plasma aldosterone was measured using a RIA kit (Coat a Count aldosterone; Diagnostic Products Corporation, Los Angeles, CA). Inulin was measured by the method of De Langhe *et al.* (7), and PAH by the technique of Brun (8). Plasma norepinephrine was measured using a specific radioenzymatic assay as described previously (9).

Statistical Analysis. Results are expressed as means ± SE. Student's *t* test was used to determine statistical significance. The Kaplan–Meier method was used to calculate

TABLE 1. CHARACTERISTICS OF PATIENTS AT BASELINE (n = 30; MEAN ± SE)

Age (years)	61.7 ± 11.4
Sex (M/F)	22/8
Pugh class	
B	19
C	11
Portocaval gradient (mm Hg)	22.8 ± 0.8
Serum bilirubin (μM)	31.0 ± 4.4
Prothrombin (INR)	1.33 ± 0.03
Serum albumin (g/L)	26.1 ± .6
Serum creatinine (μM)	121 ± 11
serum sodium (mM)	132 ± 1
Urinary sodium (mM/day)	8.0 ± 1.1

the cumulative rate of survival. Patients transplanted during follow-up were censored at the date of surgery.

RESULTS

Patient Population. Thirty-eight patients were considered for inclusion. Eight patients were excluded for the following reasons: portal vein thrombosis (n = 1), hepatocellular carcinoma (n = 1), severe liver failure (Pugh Score higher than 12; n = 2), associated Korsakoff syndrome (n = 1), and consent refusal (n = 1). One patient died before TIPS placement from an unrelated accidental death and another from cerebral hemorrhage.

Thirty patients were included. The cirrhosis was alcoholic (n = 19), viral (B virus, n = 2; C virus, n = 2) or cryptogenic (n = 5); one patient had PBC, and one hemochromatosis. Their characteristics are summarized in Table 1. In 10 patients, the medical treatment including salt-restricted diet and diuretics could not control ascites; in the remaining patients, diuretics had to be stopped due to drug-induced renal failure (n = 15), severe hyponatremia (n = 4), or hepatic encephalopathy (n = 1). All 30 patients underwent repeated multiple large-volume paracentesis during the months preceding inclusion in the study.

Previous episodes of HE were recorded in the history for 14 patients (mild HE, n = 9; moderate: n = 5) as shown in Table 2.

TIPS Procedure. The TIPS placement was successful in all 30 patients. The PCG decreased by 54% (from 22.8 ± 0.8 to 10.4 ± 0.6 mm Hg). Immediate complications were seen in five patients including transient dye-induced renal failure (n = 2), self-limited intraperitoneal bleeding (n = 2), and neck hematoma (n = 1).

TABLE 2. INCIDENCE OF HEPATIC ENCEPHALOPATHY BEFORE AND AFTER TIPS: NUMBER OF PATIENTS (%)

	Mild	*Moderate*	*Severe*	*Total*
Before TIPS	9 (30%)	5 (17%)	0 (0%)	14 (47%)
After TIPS	8 (27%)	9 (30%)	5 (17%)	22 (73%)

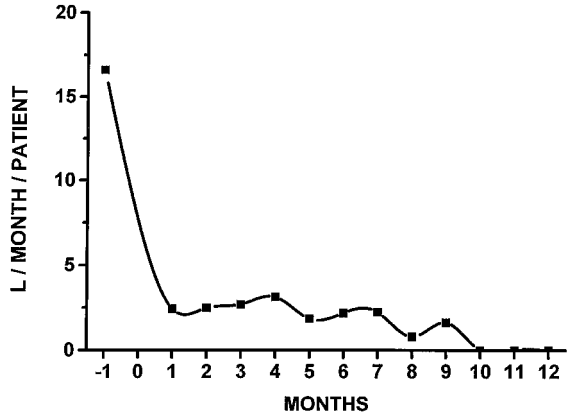

Fig. 1. Volume of paracentesis (L/month/patient) before and during the first year following TIPS.

Follow-up

Control of Ascites. Ascites disappeared in 9 patients or became easily controlled with diuretics in 17 patients after TIPS (Fig. 1). However, diuretic therapy could not be stopped in any of the responders. Weight loss usually occurred 2–6 weeks after the procedure. In three non-responders, shunt revisions induced a further decrease in the portohepatic gradient, leading to good control of ascites. In one patient, despite a marked reduction in portal hypertension (PCG, 10 mm Hg), ascites remained refractory to medical treatment. Ascites recurrence leading to large volume paracentesis associated with shunt stenosis was observed in eight patients during follow-up. Shunt revision could be performed in five patients and resulted in good control of the ascites. The clinical response could be predicted by the value of post-TIPS PCG; in responders, it was always below 16 mm Hg; in nonresponders as well as in patients in whom ascites recurred, it was always higher than 16 mm Hg, except for one patient. However, pre-TIPS Pugh score or renal function parameters were not useful predictors of successful control of ascites following treatment.

Hepatic Encephalopathy. Hepatic encephalopathy (HE) was observed in 22 patients after TIPS (Table 2) (mild, n = 8; moderate, n = 9; severe, n = 5). New-onset or worsening of HE was observed in 14 patients. Balloon occlusion of the shunt was performed in four of five patients with chronic disabling HE: HE cleared in three patients but refractory ascites recurred within days; the fourth patient died in

TABLE 3. SHORT-TERM HEMODYNAMIC AND BIOCHEMICAL EFFECTS OF TIPS

	Baseline	*After TIPS (1–2 months)*	P *value*
Portocaval gradient (mm Hg)	22.8 ± 0.8	12.1 ± 1.1	<0.01
Serum bilirubin (μM)	27.9 ± 2.8	49.2 ± 7.3	<0.01
Serum albumin (g/L)	26.2 ± 0.6	26.1 ± 1.0	NS
INR	1.34 ± 0.03	1.52 ± 0.07	<0.01
Serum creatinine (μM)	118 ± 10	104 ± 10	<0.02
Serum sodium (mM)	132 ± 1	134 ± 1	NS
Plasma norepinephrine (pg/ml)	666 ± 148	470 ± 64	NS
Plasma aldosterone (pM)*	3716 ± 841	1676 ± 307	<0.05
Plasma renin activity (ng/ml · hr)*	21.0 ± 5.2	10.5 ± 2.2	<0.05
Creatinine clearance (ml/min)*	48.9 ± 4.7	73.8 ± 8.3	<0.01
Insulin clearance (ml/min)*	57.9 ± 6.3	70.1 ± 6.5	<0.05
Urinary sodium (mmol/day)*	8.6 ± 1.5	27.1 ± 7.5	<0.01
PAH clearance (ml/min)*	347 ± 53	410 ± 48	NS

*Measured in 15 patients after a 3-day diuretic free period. Normal ranges: aldostone, 138–418 pM; plasma renin activity, 0.9–3.3 ng/ml · hr.

hepatic coma. Severe chronic HE could not be predicted using the pre-TIPS Pugh score or the TIPS-induced changes in PCG. Age, however, was a predictive factor, all patients with post-TIPS severe chronic HE being older than 65.

Survival. The mean follow-up was 265 ± 47 days. Seventeen patients died during follow-up; 3 patients underwent liver transplantation 163, 189, and 295 days following TIPS. The cumulative 1- and 2-year survivals were 41 and 34%, respectively, and were similar in cirrhotics in Pugh classes B and C (Fig. 2). The causes of death were related to liver disease in 12 patients (hepatic coma, $n = 2$; liver failure, $n = 10$) and unrelated to liver disease in 4 patients (renal failure, $n = 1$; neoplasia, $n = 1$; perforated ulcer, $n = 1$; acute respiratory distress syndrome $n = 1$). Progressive hepatic failure which was probably related to TIPS was observed in three patients. Only three patients with a Pugh score higher than 9 (class C patient) survived more than 6 months.

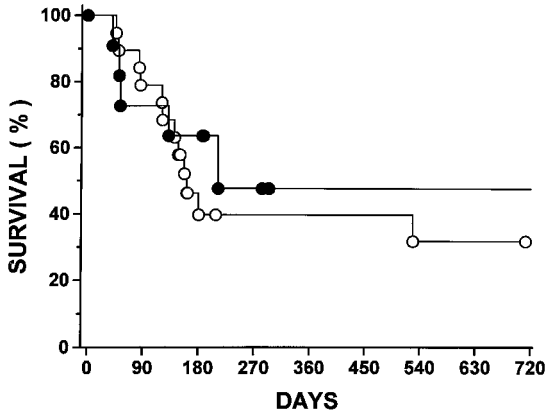

Fig. 2. Comparative cumulative survival rate after TIPS in Pugh class B (○) and C (●) cirrhotic patients with refractory ascites.

Biochemical Effects of TIPS (Table 3). Two months after TIPS, a slight deterioration of liver function was observed, as shown by an increase in serum bilirubin and prolongation of prothrombin time.

A marked decrease in plasma aldosterone and renin activity occurred, in parallel with a reduction in serum creatinine and a rise in urinary sodium excretion. Creatinine and inulin clearances improved significantly whereas PAH clearance remained unchanged. Plasma norepinephrine decreased after the procedure but the difference was not significant.

DISCUSSION

The present study shows that TIPS improved the control of ascites previously refractory to medical treatment. In a majority of patients, large volume paracentesis was no longer needed after the procedure. However, the 2-year survival rate was only 34%, which is in the same range as reported previously for patients with refractory ascites treated using other therapeutic modalities (10). Moreover, the incidence of chronic recurrent encephalopathy is high. All these findings clearly confirm that refractory ascites is often a terminal event in the evolution of liver cirrhosis.

The usefulness of TIPS in the treatment of refractory ascites is still debatable. Until now, there had been no controlled trial in the literature comparing this procedure to other methods such as repeated large-volume paracentesis with albumin infusions or Leveen shunt.

Surgical side-to-side portacaval shunts have been used in the past to improve the control of ascites (4, 5). After surgery, ascites disappears in almost all cases; however, operative mortality is high, especially in patients who belong to Pugh class C preoperatively.

The incidence of disabling encephalopathy is also a major concern. Hemodynamically, TIPS works as a side-to-side portacaval shunt, but it has some potential advantages over surgery. Operative mortality is very low because this technique can be performed without general anesthesia and laparotomy. In most cases it induces only a partial correction of portal hypertension and a certain degree of portal perfusion to the liver can be maintained; in theory, this could decrease the incidence of post-TIPS chronic hepatic encephalopathy or liver failure. On the other hand, recurrence of portal hypertension due to stenosis of the stent is frequent, occurring in 30–50% of the cases, and multiple reinterventions are needed in a significant number of patients.

The usefulness of TIPS for the treatment of refractory ascites has recently been evaluated by several groups (11–15). Overall, the studies demonstrate that this procedure allows good control of ascites in nearly 70% of the cases; it has also been shown that patients with a pre-TIPS Pugh score higher than 11 do not respond and have a poor survival rate. The onset of post-TIPS accelerated liver failure has been described in some patients. Previous experience also demonstrates that the incidence of new or worsened HE is nearly 25%. Surprisingly, chronic disabling HE is reported to be exceptional.

It is quite difficult to judge the true efficacy of TIPS from the papers published to date: the definition of refractory ascites is not uniform; and some of the treated patients already had end-stage liver failure. Most importantly, the long-term survival rate, the incidence of chronic HE or postoperative liver failure, and the rate of recurrence due to shunt stenosis are difficult to evaluate because the follow-up is short and/or a significant number of patients were transplanted within months after TIPS.

Our study showed a 2-year survival rate of 34% and a post-TIPS incidence of chronic encephalopathy of 17%. Not surprisingly, these results are quite similar to those reported after side-to-side surgical portacaval shunts (4,5). However, disabling encephalopathy occurring after TIPS can be reversed successfully using balloon occlusion of the stent in most cases (16).

In the present study, the efficacy of TIPS on the control of ascites can be partly explained by an improvement in renal function. Increases in the glomerular filtration rate and urinary sodium excretion were observed, probably related at least in part to a decrease in plasma aldosterone and renin activity and a fall in plasma norepinephrine. Similar results were reported in a recent study in which seven patients with refractory ascites were evaluated before and 1 month after TIPS insertion (15). The increase in natriuresis was limited; this could be due to worsening of peripheral vasodilatation after the procedure, possibly counteracting the natriuretic effect of the TIPS-induced reduction in sinusoidal pressure. The apparent discrepancy between the rise in GFR and the absence of changes in renal plasma flow might be explained by a preferential redistribution of flow toward the renal cortex, leading to an improvement in the coefficient of filtration.

Given the poor survival rate and the high incidence of post-TIPS disabling encephalopathy, attempts should be made to select better the patients who could benefit from the treatment. In the present study, ascites responded in a vast majority of patients. The only predictor of nonresponse was an insufficient decrease in the portohepatic gradient. However, it should be emphasized that, according to our selection criteria, patients with organic renal failure, severe hepatorenal syndrome, or end-stage liver failure were excluded. Previous papers suggest that age, previous encephalopathy, increased trail test part B, female gender, and hypoalbuminemia are independent predictors of post-TIPS severe encephalopathy (17, 18); in our experience, we observed that a majority of patients older than 65 years developed this complication.

To summarize, the results of the present prospective study demonstrate that TIPS can control refractory ascites in a majority of patients but is associated with a high rate of chronic disabling HE. In addition, a poor survival rate was observed. As refractory ascites is often a terminal event in the course of cirrhosis, liver transplantation should be considered in these patients. TIPS could be attempted in nontransplant candidates whose quality of life is severely impaired by repeated paracentesis. For transplant candidates, TIPS could be used if the waiting time is expected to be long, in order to improve the nutritional state, or to reduce the rate of complications of refractory ascites such as electrolyte imbalance, functional renal failure, and perhaps spontaneous bacterial peritonitis. However, if severe hepatic encephalopathy occurs, the shunt must be reduced or occluded; if accelerated liver failure is observed, emergency liver transplantation is mandatory.

Randomized clinical trials are needed to evaluate the exact role of TIPS in the management of refractory ascites. It is unlikely that this procedure will prolong survival but a significant improvement in the

quality of life might be demonstrated compared to established forms of therapy such as repeated large-volume paracentesis. The cost effectiveness of this new procedure must also be evaluated.

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