

Original Article

An experience with covered transjugular intrahepatic portosystemic shunt for refractory ascites from western India

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Abstract

Background: In refractory ascites/hydrothorax (RA), uncovered transjugular intrahepatic portosystemic shunt (TIPS) is shown to be superior to large-volume therapeutic paracentesis (LVP) for long-term control of ascites, but at a cost of increased risk of hepatic encephalopathy (HE). Use of covered TIPS has shown to improve shunt patency rate over uncovered TIPS. This retrospective analysis was performed on patients with RA to assess efficacy of TIPS, both covered and uncovered. **Methods:** Over 10-year period, patients with RA, patients either required LVP at least 2 times in a month, or were intolerant to LVP, or were unwilling to undergo further LVP, were treated with TIPS (Group-A = 12 patients with uncovered TIPS {Wallstent = 10, Memotherm = 1, SMART = 1}, age = 56.1 ± 4.5 years, male: female = 5:1; Group-B = 11 patients with e-PTFE-covered TIPS {Viatorr = 11}, age = 55.8 ± 5.2 years, male: female = 8:3). They were followed-up with clinical and ultrasonography/Doppler examination every monthly for 3 months and every 3 monthly thereafter (mean = 9.6 ± 4.2 months). Clinical success (disappearance of ascites at 1-month), technical success (post-TIPS reduction of portosystemic pressure gradient {PPG} < 12 mmHg), appearance of encephalopathy, TIPS-dysfunction (> 50% reduction in flow-velocity, > 50% shunt stenosis or increase in PPG > 12 mmHg in presence of symptoms) and mortality were noted. Data were analyzed using

chi-square test and t test. **Results:** Baseline clinical and biochemical characteristics were similar in both groups. TIPS placement was possible in 11/12 group-A and 11/11 group-B patients. Fall in PPG after TIPS was similar in both groups. One patient in group-A was lost follow-up after the procedure. On comparison of group-A and group-B, clinical success (63.3% and 81.8%), technical success (90.9% and 100%), occurrence of HE (60% and 54.4%) and mortality at 1-year (70% and 63.3%) were not significantly different. TIPS-dysfunction requiring re-intervention was significantly more common in group-A (50%) than group-B (0%). **Conclusions:** Covered TIPS was superior to uncovered TIPS, because of less TIPS-dysfunction without increasing chances of HE; but failed to offer any survival advantage.

Key words: Uncovered TIPS, covered TIPS, cirrhosis, refractory hepatic hydrothorax, refractory ascites

Abbreviations

Large-volume therapeutic paracentesis (LVP), transjugular intrahepatic portosystemic shunt (TIPS), hepatic encephalopathy (HE), expanded polytetrafluoroethylene (e-PTFE), portosystemic pressure gradient (PPG), hepatocellular carcinoma (HCC), international standardized ratio for prothrombin time (INR), Child-Turcotte-Pugh (CTP).

Introduction

Refractory ascites comprises of diuretic resistant ascites {less than 1.5 kg/week weight loss with low sodium diet (up to 2 g/day), Furosemide (up to 160 mg/day) and Spironolactone (up to 400 mg/day)} and diuretic intractable ascites (diuretic induced complications that preclude use of effective dose of diuretics).^{1,2} Once refractory ascites sets in, a cirrhotic patient is at high risk for developing type II hepatorenal syndrome and spontaneous bacterial peritonitis. These patients have a mortality rate of more than 50% in next 1 year.^{1,2} Hepatic hydrothorax may develop in patients with or without clinically apparent ascites. Refractory hepatic hydrothorax is defined as requirement of thoracentesis to relieve symptoms despite adequate use of diuretics.³

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Development of ascites in a cirrhotic patient is a result of development of portal hypertension with resultant splanchnic vasodilatation, renal sodium retention and reactive renal vasoconstriction.⁴ Refractory ascites is an indication of liver transplantation, which gives 1-year survival of around 85% and is the only treatment offering survival advantage.² In absence of feasibility of liver transplantation, repeated large-volume therapeutic paracentesis (LVP) and transjugular intrahepatic portosystemic shunt (TIPS) remain the major therapeutic options for such patients. Peritoneovenous shunts have problem of significant associated complications and are devoid of any effect on hepatic sinusoidal pressure, and so are largely abandoned.^{1,2} Although effective and safe in eliminating ascites, LVP does not correct hepatic sinusoidal pressure, does not obviate need of diuretics, leads to hypoproteinemia and has risk of worsening renal failure and hyponatremia if post-LVP volume expansion (ideally with albumin infusion 6-8 g/L of paracentesis) is not adequate.^{1,2} TIPS corrects increased hepatic sinusoidal pressure which is the basic pathogenetic mechanism of refractory ascites. TIPS also improves renal function and obviates need for diuretics. In addition to procedural complications, TIPS has problems of new-onset or worsening hepatic encephalopathy (HE) and worsening liver dysfunction.^{1,2}

In the World literature, there are 3 meta-analyses using all the five available randomized trials on the use of uncovered TIPS and LVP in refractory ascites.⁵⁻¹² Uncovered TIPS is shown to be superior to LVP for long-term control of ascites thus effective in reducing the need for repeated large-volume paracentesis;^{4-7,13} but data on survival benefit for uncovered TIPS is controversial. Uncovered TIPS had no effect on transplant-free survival,^{10,12} or overall survival¹² Survival was significantly better in TIPS group in two trials,^{9,11} but worse in the oldest trial.⁸ Overall, 2 meta-analyses failed to show any survival advantage for uncovered TIPS,^{5,7} but one meta-analysis showed a trend toward improved survival without any significant heterogeneity after exclusion of an outlier trial (Lebrech D et al).^{6,8} Also Cochrane meta-analysis including 4 trials^{8-10,12} showed statistically significant survival benefit for uncovered TIPS, but with unexplained heterogeneity.¹⁴ Cost-effectiveness and effect on quality of life were not checked in these meta-analyses;⁵⁻⁷ a trial by Gines P, et al showed higher costs for TIPS group,¹⁰ and trial by Sanyal AJ, et al failed to show improvement in quality of life.¹² Although incidence of HE was increased in TIPS group,⁵⁻⁷ but difference was not as dramatic as seen in the studies using TIPS for variceal bleeding;¹³ as refractory ascites itself reflects more advanced liver disease which is itself a risk factor for HE irrespective of the treatment received.¹³ There is reduced incidence of HRS in those receiving TIPS.^{10,12} Another major problem after use of uncovered TIPS is shunt stenosis which occurs in 40-70% over 1 year and 70-85% at 2 years.^{5-7,15} Optimal PPG needed for

control of variceal haemorrhage is less than 12 mmHg to prevent rebleeding, such figure for refractory ascites is not established clearly; but thought to be less than 8 mmHg.^{4,12}

In various small series, TIPS either reduces need of thoracentesis or leads to resolution of hepatic hydrothorax.^{4,13} Use of TIPS in HRS is investigatory at present.⁴ In an uncontrolled trial, post-TIPS survival for type II HRS was 45% at 1 year and was better than HRS type I.^{4,13,16}

Covered TIPS stents have antithrombotic property and avoids hyperplasia of the pseudointima growing inside the stent.¹⁷ Use of covered TIPS has shown to improve shunt patency rate over uncovered TIPS, thus requiring fewer reinterventions.^{17,18} Covered TIPS does not increase incidence of HE, contrary to common belief that uncovered TIPS has lower HE because shunt size reduction due to pseudointimal proliferation.¹⁷ There are trials comparing uncovered TIPS and covered TIPS in mixed indications; none of these trials have exclusively looked at refractory ascites as an indication for TIPS,¹⁷⁻²⁰ which seems necessary, because compared to variceal haemorrhage, refractory ascites develops in presence of more advanced liver disease, which itself constitutes poor outcome factor for TIPS procedure.

This study was planned to assess efficacy of TIPS (both uncovered and covered) on patients with either required LVP at least 2 times in a month, or were intolerant to LVP, or were unwilling to undergo further LVP.

Methods

Study design

This single-centre retrospective analysis was carried out at Bombay Hospital, Mumbai, India. It included all the consecutive patients with cirrhosis (excluding Budd-Chiari syndrome) over last 10 years (1996-2005); who underwent TIPS for refractory ascites/hepatic hydrothorax. Patients either required LVP at least 2 times in a month, or were intolerant to LVP, or were unwilling to undergo further LVP. Exclusion criteria were usual contraindications for TIPS: presence of ongoing sepsis, ongoing biliary obstruction, multiple hepatic cysts, large central hepatic tumours, thrombocytopenia of 20,000 platelets/cmm, portal vein thrombosis, congestive cardiac failure, severe tricuspid regurgitation, and severe pulmonary hypertension.

Study protocol

Study population was divided in to two groups: 1) Group A comprised of patients treated with uncovered TIPS {In this group, 10 patients received Wallstent, Boston Scientific, Barcelona, Spain; 1 patient received Memotherm, Bard-Angiomed, Karlsruhe, Germany; 1 patient received SMART} during period from 1996 to

2001 (n = 12 of which 1 was unsuccessful); 2) Group B comprised of patients treated with expanded-polytetrafluoroethylene (e-PTFE) covered TIPS {In this group, 11 patients received Viatorr Endoprosthesis, W. L. Gore & Associates, Flagstaff, Ariz. USA} during period from 2002 to 2005 (n = 11). Patency of TIPS was checked with Doppler studies after 24 hours of the TIPS procedure. All the patients were called for follow up every monthly for initial 3 months and then every 3 months till treatment end-points (described in the following section) or till December 2005. During each follow up visit, detailed history, clinical examination, blood biochemistry (including complete blood count, liver function tests and renal function tests), ultrasonography of abdomen with Doppler studies for hepatic-portal venous system and TIPS angiography (as and when required) were carried out as a part of protocol. When ultrasonography Doppler study suggested TIPS dysfunction or there is a recurrence of a complication of portal hypertension, then TIPS angiography with pressure measurement was performed. In case of TIPS dysfunction, patency was re-established either with re-canalization by balloon angioplasty or with revision TIPS (insertion of coaxial/ parallel stent of same type).

Definitions of end-points

- Clinical success: Complete disappearance of ascites/hydrothorax at 1 month post-TIPS
- Technical success: Creation of a channel by stent between hepatic vein and portal vein to reduce the portosystemic pressure gradient (PPG) to less than 12 mmHg
- Early mortality: Deaths occurring within 1 month of TIPS
- Late mortality: Deaths occurring during study period after 1 month of TIPS
- TIPS dysfunction: 50% decrease in portal vein blood flow velocity on Doppler, angiographic evidence of stent stenosis (> 50% reduction in diameter) or increase in PPG > 12 mmHg in presence of recurrence of ascites/hepatic hydrothorax or gastrointestinal bleeding
- Primary patency: Duration of continuous TIPS patency without re-intervention
- Assisted patency: Duration of continuous TIPS patency with or without re-intervention

Statistical analysis

Data were analyzed using chi-square test and student t test. Further subgroup analysis {group A1 (uncovered TIPS) – n = 6, group B1 (covered TIPS) – n = 7} was carried out after applying strict exclusion criteria: presence of hepatocellular carcinoma (HCC), presence of upper gastrointestinal bleeding within 6 weeks, Child-Turcotte-Pugh (CTP) score > 11, Creatinine > 2 mg/dL, Bilirubin >

3 mg/dL and international standardized ratio for prothrombin time (INR) > 2.

Results

Baseline characteristics

In addition to features tabulated in *Table I*, indications for doing TIPS were as follows: 1) refractory ascites in 11 patients (91.6%) of group A [including 3 patients (27.2%) with diuretic intolerant type] and in 9 patients (81.8%) of group B [including 2 patients (22.2%) with diuretic intolerant type]; 2) refractory hepatic hydrothorax in 1 patient (8.4%) of group A and 2 patients (18.2%) of group B. Aetiologies of cirrhosis were as follows: 1) alcohol in 3 patients (25%) of group A and 4 patients (36.3%) of group B; 2) Hepatitis B in 2 patients (16.6%) of group A and in 2 patients (18.2%) of group B; 3) Hepatitis C in 5 patients (41.6%) of group A and 4 patients (36.3%) of group B; 4) Cryptogenic in 2 patients (16.6%) of group A and 1 patient (9.1%) of group B. None of the patients (0%) had Budd-Chiari syndrome as an underlying cause for refractory ascites. None of the patients had Child's class A. None of the patients in either group had presence of HE at the time of TIPS. Baseline clinical and biochemical characteristics were comparable in both the groups.

Characteristics of TIPS placement

TIPS placement was possible in 11/12 patients (91.6%) of group A (In one patient in group A cannulation of internal jugular vein failed for anatomical reasons) and in 11/11 patients (100%) of group B. Detailed comparison of clinical as well as technical success and changes in PPG after TIPS placement is shown in *Table II*. There was no significant difference between the two groups. In group A, 7 patients (63.6%) achieved post-TIPS PPG of 8 mmHg compared to 8 patients (72.7%) in group B.

Follow up data

One patient in group-A was lost to follow-up after the procedure within 1 week. As shown in *Table III*, on comparison of patients of group-A (10 patients) vs group-B (11 patients), (on whom follow up was available) clinical success, technical success, occurrence of HE or resistant HE and mortality at 1-year were not significantly different. Only in one patient of group B reduction in size of TIPS was performed because of resistant HE, which improved HE in that patient. In other patients resistant HE was result of progressive deteriorating liver failure and was terminal event. Recurrence of ascites as a result of TIPS dysfunction was significantly more common in group-A (5 patients, 50%) than group-B (0 patient, 0%), and so primary patency rate was lower in group A. In group A, balloon re-canalization was performed in 2 pa-

Table I. Baseline characteristics of both the groups.

Characteristics	Group A	Group B	P value
Numbers	12	11	-
Age, years	56.1 ± 4.5	55.8 ± 5.2	NS
Sex (M:F)	10:2	8:3	NS
Child-Pugh-Turcotte score	10.1 ± 0.5	9.36 ± 0.4	NS
Child class A/B/C %	0/58.4/41.6	0/45.5/54.5	NS
Past hepatic encephalopathy	0 (0%)	1 (9.1%)	NS
Past variceal bleeding	3 (25%)	4 (36.3%)	NS
Hepatorenal syndrome type II	3 (25%)	4 (36.3%)	NS
Hepatocellular carcinoma	0 (0%)	2 (18.2%)	NS
S. Bilirubin mg/dL	1.6 ± 0.8	1.9 ± 0.7	NS
S. Albumin gm/dL	2.7 ± 0.9	2.9 ± 0.4	NS
S. Creatinine	1.2 ± 0.3	1.6 ± 0.5	NS
Prothrombin time > control seconds	4.4 ± 1.2	5 ± 1.3	NS
S. Sodium	130.5 ± 5	131.9 ± 5.4	NS

Table II. characteristics of TIPS placement in both the groups.

Successful TIPS placement	Group A	Group B	P value
Numbers	11	11	-
Clinical success	7 (63.3%)	9 (81.8%)	NS
Technical success	10 (90.9%)	11 (100%)	NS
Pre-TIPS PPG, mmHg	26.14 ± 0.3	24.45 ± 2.2	NS
Post-TIPS PPG, mmHg	8.14 ± 2.5	5.72 ± 0.8	NS
Fall in PPG after TIPS, mmHg	17 ± 2.2	15.7 ± 2	NS

Table III. Characteristics of follow up of both the groups.

Available follow up	Group A	Group B	P value
Numbers	10	11	-
Follow up, months	8.4	12.8	-
Hepatic encephalopathy/	6 (60%)/	6 (54.5%)/	NS/
Resistant encephalopathy, n (%)	4 (40%)	4 (36.3%)	NS
Variceal bleeding, n (%)	1 (10%)	0 (0%)	NS
Recurrence of ascites, n (%)	5 (50%)	1 (9.1%)	S
TIPS dysfunction, n (%)	5 (50%)	0 (0%)	S
Re-intervention done, n (%)	4 (40%)	0 (0%)	S
Primary patency rate at 6-month	50%	90.9%	S
Assisted patency rate at 6-month	70%	90.9%	NS
Early mortality, n (%)	0 (0%)	2 (18.2%)	NS
Mortality at 12 months, n (%)	7 (70%)	7 (63.6%)	NS
Liver-related mortality, n (%)	6 (60%)	5 (45.4%)	NS
Corrected mortality rate at 1-year after applying strict exclusion criteria (%)	50% (group A1: 6 patients)	42.8% (group B1: 7 patients)	NS

tients and revision TIPS in the same track was performed in 2 patients and one patient refused for any re-intervention. In the group B, one patient had developed ascites as a result of progressive liver failure which ultimately resulted in death of the patient; TIPS angiography in that patient demonstrated patent TIPS stent, and so did not require any re-intervention. Of the patients with TIPS dysfunction, two patients in group A and none of group B had acute thrombosis of TIPS which required re-canalization. Assisted patency was statistically not different in any of the groups. None of the patient had TIPS-procedure-relat-

ed complications. Two patients, including one with multicentric peripheral HCC, had early mortality in group B due to progressive deteriorating liver function. There was no significant difference between both groups in 1-year mortality, liver related mortality and corrected mortality rates. After applying strict exclusion criteria, there was trend towards improvement in mortality rates in group A (from 70% to 50%) and group B (from 63.6% to 42.8%), but difference was not statistically significant. Only three patients of group B were alive at end of 2 years post-TIPS, whereas none in the group A. Major cause of death

in both the groups was progressive liver failure (7 patients in group A and 6 patients in group B); three other patients in group A and two other patients in group B died of sepsis.

Discussion

This preliminary study is one of the earliest reports from India on use of covered TIPS for refractory ascites. In present study, covered TIPS was found to be superior to uncovered TIPS, because of less TIPS-dysfunction without increasing chances of hepatic encephalopathy; but failed to offer any survival advantage.

Although a retrospective analysis, the present study had several strengths. Both the groups were statistically comparable at baseline. There was no difference in the parameters known to be associated with TIPS outcome like age, sex, aetiology of liver disease, serum bilirubin, serum creatinine, INR, serum proteins, past HE, indication of TIPS placement and CPT score. The study was carried out at a single centre using a procedure-related treatment on comparable groups, with exception of using different stent designs in the uncovered TIPS group. There is no data in the World literature favouring a particular uncoated TIPS stent which can make difference in efficacy or safety of TIPS.¹⁷

In the World literature, success rate with TIPS placement is more than 90% in most series.^{4,13} Technical success can be achieved in 95% and clinical success can be achieved in 90% of cases.⁴ Our results were in accordance to the literature.

Early mortality is reported to be as high as 55% in the literature as a result of poor patient selection in earlier series and in most situation, death was caused by underlying progressive liver disease rather than complications of TIPS.⁴ TIPS related major complications (like intra-abdominal bleeding, hepatic artery or portal vein laceration and congestive heart failure) are expected in no more than 3% of cases.⁴ Procedure related mortality rates are around 1%.^{4,13} In present series, none of the patient had such complications.

One-year mortality rates when indication is refractory ascites are 48-76%.⁴ Survival after TIPS is best predicted from models using different parameters like serum bilirubin, serum creatinine, INR, serum alanine aminotransferase, pre-TIPS encephalopathy, urgency of TIPS, aetiology of cirrhosis and CTP score.⁴ Both the groups in the present series were comparable for above parameters; there was no difference in early mortality, 1-year mortality or liver-related mortality. 1-year survival rates were above 60% in both the groups when all the patients were taken in account, but fell down to around 50% when careful patient selection was applied. As, in a cirrhotic, serum bilirubin level > 3 mg/dL and INR > 2 indicates severe liver failure in absence of cholestasis and serum creatinine level > 2 mg/dL denotes presence of type II HRS; outcome of TIPS in a patient with refractory ascites and such

profile remains poor. For optimal outcome following TIPS, ideal patient should be patients of refractory ascites with relatively preserved hepatic and renal function.²¹

Major problems after TIPS are the occurrence of hepatic encephalopathy and shunt dysfunction.

30-70% patients had shunt dysfunction within 1 year, resulting in recurrence of variceal bleeding or ascites and in high re-intervention rate.²² TIPS dysfunction is due to thrombosis or pseudointimal hyperplasia. TIPS thrombosis occurs early within 3 weeks and frequency is 10-15%, to prevent this routine use of anticoagulation is not recommended and it is best treated with radiological intervention.^{4,13,17} In the present series, only 2 of 21 patients (9.5%) experienced acute thrombosis of TIPS, both in uncovered TIPS group. Shunt stenosis due to pseudointimal hyperplasia occurs in 18-78% of uncovered TIPS depending on surveillance technique used.^{4,13} Doppler studies have variable sensitivities and specificities ranging from 70% to 100% in diagnosis of TIPS dysfunction.¹³ Abnormal Doppler ultrasound is predictive of occlusion or stenosis, whereas normal ultrasound does not exclude TIPS dysfunction; so best indicator of TIPS dysfunction is a recurrence of the problem for which the TIPS was originally inserted.⁴ In the present series, three patients of uncovered TIPS group and none of covered TIPS group had shunt stenosis due to pseudointimal hyperplasia, all were detected by Doppler studies and was confirmed later by TIPS angiography. Covered stent leads to reduction of thrombosis and pseudointimal hyperplasia thereby improving TIPS long-term patency, maintaining lower PPG and reducing requirement of re-intervention. With covered TIPS (e-PTFE stent-graft) primary patency rates range from around 80% to 90% within 1 year and secondary patency rate is nearly 100%.^{4,17-20} In present series, there was not a single case of TIPS dysfunction in covered TIPS group.

The incidence of new or worsening HE following TIPS is on average 20-31%, but ranges widely from 3% to 75%.^{1,15} In various trials, pre-TIPS factors associated with post-TIPS HE are aetiology of liver disease other than alcohol, female sex, hypoproteinemia, old age, past episodes of HE and ongoing HE at time of TIPS.⁴ In the present study, overall incidence of HE was 57.1% (12/21 patients), most of them was part of terminal progressive liver failure. Both the groups were comparable in terms of parameters that predict occurrence of HE, and both had comparable incidence of HE. In most patients, HE responds to medical therapy, only in around 5% cases TIPS reduction or occlusion is required.⁴ In the present study, only one patient required, reduction in TIPS diameter to control resistant HE.

In the present study, covered TIPS was superior to uncovered TIPS, because of less TIPS-dysfunction without increasing chances of HE covered stents result in fewer interventions which may then improve cost effectiveness with lesser recurrence of ascites. Further randomized con-

trolled trials are needed to confirm these findings and to check survival advantage, cost-effectiveness and effect on quality of life.

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