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Transjugular Intrahepatic Portosystemic Shunts With Covered Stents Increase Transplant-Free Survival of Patients With Cirrhosis and Recurrent Ascites

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BACKGROUND & AIMS: There is controversy over the ability of transjugular intrahepatic portosystemic shunts (TIPS) to increase survival times of patients with cirrhosis and refractory ascites. The high rate of shunt dysfunction with the use of uncovered stents counteracts the benefits of TIPS. We performed a randomized controlled trial to determine the effects of TIPS with stents covered with polytetrafluoroethylene in these patients. **METHODS:** We performed a prospective study of 62 patients with cirrhosis and at least 2 large-volume paracenteses within a period of at least 3 weeks; the study was performed at 4 tertiary care centers in France from August 2005 through December 2012. Patients were randomly assigned to groups that received covered TIPS (n = 29) or large-volume paracenteses and albumin as necessary (LVP+A, n = 33). All patients maintained a low-salt diet and were examined at 1 month after the procedure then every 3 months until 1 year. At each visit, liver disease–related complications, treatment modifications, and clinical and biochemical variables needed to calculate Child-Pugh and Model for End-Stage Liver Disease scores were recorded. Doppler ultrasonography was performed at the start of the study and then at 6 and 12 months after the procedure. The primary study end point was survival without a liver transplant for 1 year after the procedure. **RESULTS:** A higher proportion of patients in the TIPS group (93%) met the primary end point than in the LVP+A group (52%) ($P = .003$). The total number of paracenteses was 32 in the TIPS group vs 320 in the LVP+A group. Higher proportions of patients in the LVP+A group had portal hypertension-related bleeding (18% vs 0%; $P = .01$) or hernia-related complications (18% vs 0%; $P = .01$) than in the TIPS group. Patients in LVP+A group had twice as many days of hospitalization (35 days) as the TIPS group (17 days) ($P = .04$). The 1-year probability of remaining free of encephalopathy was 65% for each group. **CONCLUSIONS:** In a randomized trial, we found covered stents for TIPS to increase the proportion of patients with cirrhosis and recurrent ascites who survive transplantation-free for 1 year, compared with patients given repeated LVP+A. These findings support TIPS as the first-line intervention in such patients. ClinicalTrials.gov ID: NCT00222014.

Keywords: Liver Fibrosis; TIPS; Refractory Ascites; PHT.

Refractory or recurrent ascites is a severe complication of cirrhosis, with a mean 1-year survival rate of 50%.[1,2] Patients could benefit from liver transplantation, but <20% of them will receive transplants because of contraindication or advanced age. Another therapeutic option is repeated large-volume paracentesis with albumin (LVP+A) infusion. However, the underlying liver disease is not improved and clinical outcomes remain dismal.[3,4] Portal hypertension (PHT) is the main determinant of ascites, and decreasing portal pressure by portosystemic shunt has been shown to relieve ascites.[5]

Randomized controlled trials (RCT) on transjugular intrahepatic portosystemic shunt (TIPS) vs LVP in patients with refractory ascites showed an important reduction of recurrence of tense ascites in patients allocated to TIPS.[6–10] However, all of those studies were performed with uncovered stents, leading to a high rate of shunt dysfunction, which was the main drawback of this treatment.[6–11]

The development of polytetrafluoroethylene (PTFE)-covered stents was considered major progress in this field, owing to a substantial decrease in the rate of shunt dysfunction and to an improvement in clinical outcomes.[12–15] Furthermore, the selection of patients for TIPS has been shown to be crucial in order to observe a potential gain in term of survival.[10] Actually, an improved 1-year survival rate was demonstrated using covered stents in highly selected patients with cirrhosis and variceal bleeding.[16] We therefore hypothesized that both accurate selection[17] and the use of covered stents should improve the prognosis for patients with cirrhosis and recurrent ascites treated by TIPS.

Abbreviations used in this paper: **LVP+A, large-volume paracentesis with albumin; OHE, overt hepatic encephalopathy; PHT, portal hypertension; PPG, portal pressure gradient; PTFE, polytetrafluoroethylene; RCT, randomized controlled trials; TFS, transplantation-free survival; TIPS, transjugular intrahepatic portosystemic shunt.**

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The present RCT in patients with cirrhosis and recurrent ascites aimed to compare the efficacy of covered TIPS to LVP+A in terms of liver transplantation-free survival (TFS).

Methods

Study Design

Between August 2005 and December 2012, patients with cirrhosis and at least 2 LVPs within a minimum interval of 3 weeks were considered for inclusion.

Inclusion criteria were patients with cirrhosis, as documented by previous liver biopsy or a combination of usual clinical and biochemical signs; age older than 18 years and younger than 70 years; recurrent tense ascites; and signed informed consent form.

Exclusion criteria were patients who had required >6 LVPs within the previous 3 months; patients expected to receive transplants within the next 6 months or on waiting list; usual contraindications for TIPS, congestive heart failure, history or presence of pulmonary hypertension, complete portal vein thrombosis, recurrent overt hepatic encephalopathy (OHE), hepatocarcinoma, severe liver failure (defined by prothrombin index <35% or total bilirubin >100 μmol/L or Child-Pugh Score >12), serum creatinine >250 μmol/L, uncontrolled sepsis, known allergy to albumin, pregnant or breastfeeding women, refusal to participate, or patient unable to receive information or to sign written informed consent.

All patients provided written informed consent. The study protocol was approved by the local ethics committee (CCPPRB Toulouse II). Three centers were closed and replaced by 3 others because of noncompliance with good research practice and guidelines (the patients included in those centers were not analyzed) or no effective inclusion. Accordingly, the patients considered for analysis were included in Toulouse, Paris, Lille, and Angers.

The main end point was 1-year liver TFS. Secondary end points were ascites recurrence and treatment failure as defined here, the rate of OHE, PHT-related complications, other complications of cirrhosis, and the number of days in hospital during a 1-year period after inclusion.

Treatment Procedures

Diagnostic evaluation before randomization included clinical assessment of cirrhosis complications, usual blood tests, Doppler ultrasonography of the abdomen, and echocardiography to rule out exclusion criteria. After the investigator received written informed consent, randomization was generated online by computer, equilibrated for each center, stratified according to whether cirrhosis was alcoholic or not and adjusted every 10 patients. TIPS was performed under sedation as described previously.[13] For homogeneity reasons, technical recommendations for TIPS placement were as follows: a 10-mm covered stent was used (Viatorr; TIPS endoprosthesis, W.L. Gore & Associates, Inc, Flagstaff, AZ), dilated to 8 or 10 mm Hg according to the hemodynamic response. The aim was to reduce portal pressure gradient (PPG) <12 mm Hg.

Follow-Up

All patients were maintained on a low-salt diet. Patients had a clinical examination at 1 month and then every 3 months up to 1 year. At each visit, liver disease-related complications, treatment modifications, and clinical and biochemical variables needed to calculate Child-Pugh and Model for End-Stage Liver Disease scores were recorded. Doppler ultrasonography was performed at the beginning, and 6 and 12 months after. Patients were followed for 1 year or until liver transplantation or death.

Patients included in the LVP+A group were treated by LVP+A whenever required. Eight grams albumin per liter ascites extracted were infused when >3 L ascitic fluid had been removed. The use of diuretics was allowed at the maximal tolerated dose and compliance with low-sodium diet was assessed by direct questioning and natriuresis. In the group treated by LVP+A, failure was defined as the need for >6 LVPs within 3 months and alternative treatment, mainly TIPS or liver transplantation could be proposed. All of these patients with treatment failure were to be followed up to 1 year after inclusion. In the TIPS group, the relapse of ascites requiring at least 2 LVPs or its persistence after 2 months were considered as failure. When shunt dysfunction was suspected because of relapse of ascites or incomplete response 2 months after the procedure, an angiography with a PPG measurement was performed. If shunt dysfunction was confirmed, angioplasty or PTFE re-stenting aiming to reduce PPG <12 mm Hg were performed.

Statistical Analyses

The initial sample calculation, based on available published data in 2004, was 60 patients per group. During the course of the study, a 52% 1-year TFS among patients treated by LVP+A infusion was reported by a meta-analysis[18] and 2 studies[9,10] found an 80% 1-year TFS survival rate in patients treated by TIPS with uncovered stents. Accordingly, the number of patients needed for our study was recalculated based on the following updated hypotheses: 1-year TFS rate of 85% among patients treated with PTFE-covered stent and 52% among those treated by LVP+A. To detect such a difference, a minimum of 30 patients per group was needed (2-sided test, $\alpha = .05$ and $\beta = .2$), adjusted for a 5% loss of follow-up.

The SPSS statistical package (SPSS Inc, Chicago, IL) was used for the analysis according to an intention to treat strategy. Comparisons between the 2 groups were performed using Student t test or χ^2 test, as required. Actuarial probability curves were constructed using the Kaplan–Meier method and compared with the log-rank test. Patients in the LVP+A group who were switched to TIPS treatment were censored alive at the time of the shunt procedure for the TFS analysis. Cox regression analysis was used to identify independent predictors for the primary end point. Statistical significance was established at $P < .05$.

All authors had access to the study data and reviewed and approved the final manuscript.

Results

Patients' Characteristics

Among the 137 patients admitted for recurrent ascites during the study period, 62 patients were included. Reasons for excluding the other 75 patients are listed in Supplementary Figure 1. Of the 62 included patients, 29 were enrolled in the TIPS group and 33 in the LVP+A group. The baseline characteristics of the patients were similar in

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