Research Article

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Use of early-TIPS for high-risk variceal bleeding: Results of a post-RCT surveillance study

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Background & Aims: In a recent randomized international clinical trial (RCT) in high-risk cirrhotic patients with acute variceal bleeding, the early use of transjugular intrahepatic portosystemic shunt (TIPS) was associated with marked and significant reductions in both treatment failure and mortality. The aim of this study was to confirm these results in clinical practice in the same centers of the RCT study.

Methods: We retrospectively reviewed patients admitted for acute variceal bleeding and high risk of treatment failure (Child C <14 or Child B plus active bleeding), treated with early-TIPS (n = 45) or drugs + endoscopic therapy (ET) (n = 30).

Results: Patients treated with early-TIPS had a much lower incidence of failure to control bleeding or rebleeding than patients receiving drug + ET (3 *vs.* 15; p <0.001). The 1-year actuarial probability of remaining free of this composite end point was 93% *vs.* 53% (p <0.001). The same was observed in mortality (1-year actuarial survival was 86% *vs.* 70% respectively; p = 0.056). Actuarial curves of failure to control bleeding + rebleeding and of survival were well within the confidence intervals of those observed in the RCT.

Conclusions: This study supports the early use of TIPS in patients with cirrhosis and a high-risk variceal bleeding.

Keywords: Liver cirrhosis; Portal hypertension; Prognosis; Treatment.

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Abbreviations: AVB, acute variceal bleeding; PTFE, polytetrafluoroethylene; ET, endoscopic treatment; HE, hepatic encephalopathy; HVPG, hepatic venous pressure gradient; PPG, portal-venous pressure gradient; RCT, randomized international clinical trial; TIPS, transjugular intrahepatic portosystemic shunt.

Introduction

In patients with cirrhosis, acute variceal bleeding (AVB) is one of the most dreadful complications [1]. Over the past decades, improvements in the management of AVB have been associated with a reduction in treatment failure and mortality. However, despite the application of the current gold standard therapy, consisting in the combination of early vasoactive drugs, prophylactic antibiotics, and therapeutic endoscopic procedures [2,3], there is still a 10–20% treatment failure and approximately 10% mortality. Remarkably, these complications occur mainly in a relatively small group of patients considered as a high-risk population. These patients are usually identified on the basis of clinical and biochemical characteristics (such as the Child-Pugh score, and activity of bleeding despite vasoactive drug infusion) or hemodynamic findings (such as a HVPG over 20 mmHg) [4,5]. In a recent randomized international clinical trial (RCT), in high-risk patients with cirrhosis and acute variceal bleeding, the early creation of a transjugular intrahepatic portosystemic shunt (TIPS) with the use of stents covered with polytetrafluoroethylene (e-PTFE) is associated with marked and significant reductions in both treatment failure and mortality. In addition, the incidence of other complications of portal hypertension, such as ascites, is also reduced [6]. The aim of the present surveillance study was to assess whether these excellent results are similar in clinical practice outside RCTs.

Materials and methods

Patients

We conducted a retrospective review of all patients admitted for acute variceal bleeding and at high risk of treatment failure (defined by Child C <14 or Child B plus active bleeding at endoscopy despite intravenous vasoactive drug treatment, as in the RCT) at the centers participating in the original RCT on the use of early TIPS. Active variceal bleeding at endoscopy was defined on the basis of the Baveno criteria [7]. The patients included in the study were those hospitalized over a period of time between the inclusion of the last patient in the RCT (March

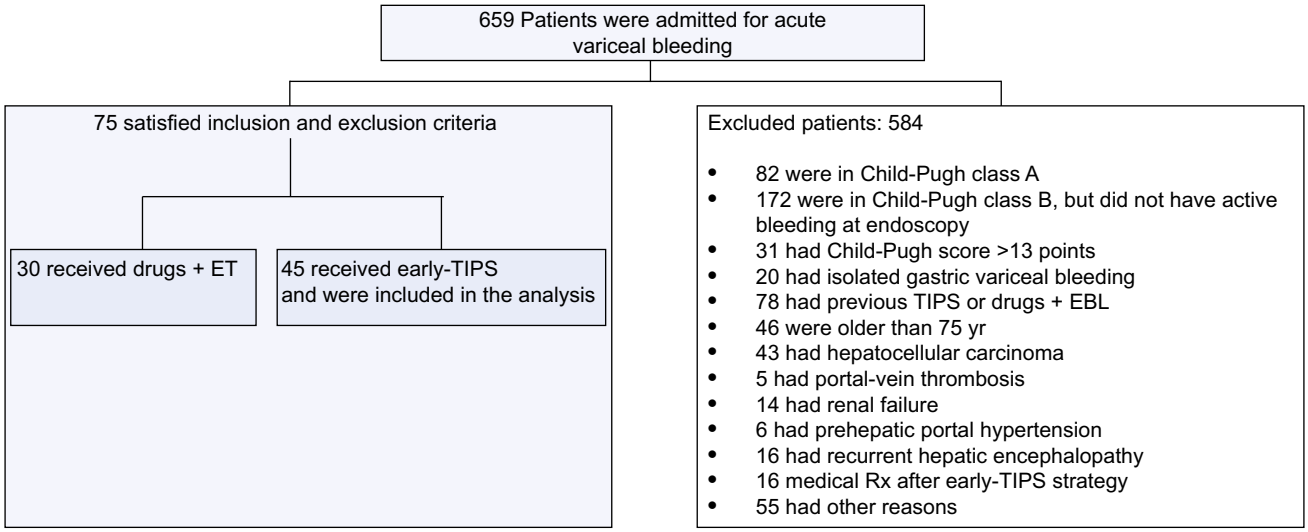

Fig. 1. Screening and randomization of patients.

2007) and January 2011. The acute esophageal variceal bleeding was treated with a combination of vasoactive drugs, endoscopic treatment, and prophylactic antibiotics. Endoscopic treatment (ET) was applied at the time of diagnostic endoscopy, performed within 12 h after admission, while patients were already receiving vasoactive drugs. Exclusion criteria were those of the RCT study: age more than 75 years, pregnancy, hepatocellular carcinoma that did not meet the Milano criteria, a creatinine level greater than 3 mg per deciliter (265 μmol per liter), previous pharmacologic therapy combined with endoscopic treatment or PTFE–covered TIPS to prevent rebleeding, bleeding from isolated gastric or ectopic varices, total portal-vein thrombosis, recurrent hepatic encephalopathy and heart failure.

To avoid a possible selection bias, patients receiving medical therapy with standard of care treatment (vasoactive drugs plus EBL and prophylactic antibiotic) were included only until the moment when each individual center decided to adopt the strategy of using early-PTFE–covered TIPS for all high-risk patients (n = 30). Change in treatment strategy was different in time and on implementation. Indeed, some centers changed just after the results were analyzed for the first abstract, while others required the acceptation of the scientific community (full paper published). Since then, patients treated with early-PTFE–covered TIPS were included (n = 45).

Patients were followed until death or liver transplantation, up to a maximum of 2 years of follow-up, or until the end of the study (March 2011).

Medical arm

Treatment with vasoactive drugs was continued until patients were free of bleeding for at least 24 h, preferably up to 5 days; then a non-selective beta-blocker (either propranolol or nadolol) was started and titrated as previously described [6]. Some of the patients (n = 6) also received isosorbide-5-mononitrate (20 mg twice a day or the maximum tolerated dose). In addition, within 7–14 days after the initial endoscopic treatment, endoscopic band ligation (EBL) was performed. EBL sessions were then scheduled until variceal eradication was achieved, as previously described [6]. After eradication, endoscopic monitoring was performed and if varices reappeared, further EBL sessions were initiated. Treatment failure was defined as one severe rebleeding episode (i.e., requiring a transfusion of more than 2 units of blood) or two, less severe rebleeding episodes. TIPS and placement of a PTFE–covered stent were used as rescue therapy when necessary.

Early-PTFE–covered TIPS

TIPS was performed within 72 h of the initial endoscopy (whenever possible, within the first 24 h), and vasoactive drugs were administered until then. The PTFE–covered stents (Viatorr TIPS endoprosthesis, Gore) were initially dilated to 8 mm. If the portal-pressure gradient (the difference between portal-vein pressure and inferior vena cava pressure) did not decrease below 12 mmHg, the stent was dilated to 10 mm.

TIPS revision was performed if there was clinical recurrence of portal hypertension or evidence of TIPS dysfunction at Doppler ultrasonography, as previously defined [6]. If TIPS dysfunction was confirmed, angioplasty was performed or another PTFE–covered stent was placed.

Study end points

As in the RCT, the primary end point of the study was a composite outcome of failure to control acute bleeding or to prevent clinically significant variceal rebleeding. Secondary end points were mortality, the development of other complications related to portal hypertension and the percentage of follow-up days spent in hospital.

Statistical analysis

Statistical analysis was performed with SPSS 19 statistical software package (SPSS, Chicago, IL) and *R* (http://www.r-project.org). Comparisons between patients treated with early-TIPS or medical therapy were performed with unpaired Student's *t*-test, Mann–Whitney test or Fisher's exact test as appropriate. The risk failure to control bleeding or rebleeding was described with the cumulative incidence function (CIF) taking into account death or liver transplantation as competing risks. A similar strategy was followed for the risk of hepatic encephalopathy and ascites. The risk of death was estimated with the CIF taking into account liver transplantation as competing risk. This provides more accurate estimations of rebleeding and mortality rates than censoring patients at the time of death/liver transplantation in a Kaplan–Meier analysis [8]. Comparisons between treatment groups were performed with the Gray test [9]. Competing risks analysis was performed with the *R* package *cmprsk*, with the aid of the Cum-Incidence function developed by Scrucca *et al.* [10].

Results

Study patients

A total of 659 patients with acute variceal bleeding were admitted to the participating hospitals, of which 584 had exclusion criteria for the study (Fig. 1). The remaining 75 patients received either the standard medical therapy (30 patients) or early-PTFE–covered TIPS (45 patients). There were no significant differences in baseline characteristics between the two groups at the time of study entry (Table 1). The mean (±SD) follow-up period was 14.6 ± 12 months in the medical group and 13.1 ± 12 months in