Early TIPS to Improve Survival in Acute Variceal Bleeding
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Gastroesophageal varices are present in 50% of patients with cirrhosis, and variceal hemorrhage develops in up to one third of these patients. The risk of variceal hemorrhage is increased in patients who have large varices and advanced stages of liver disease, as assessed on the basis of the Child–Pugh class. Several studies published between 1942 and 1981 showed poor outcomes after variceal hemorrhage, with mortality rates of 40% at 6 weeks and 70% at 1 year. Over the past five decades, a number of randomized trials have shown an improvement in the efficacy of endoscopic, pharmacologic, surgical, and radiologic techniques for arresting hemorrhage, but most of these studies were not powered to determine whether these therapies resulted in a survival benefit. Subsequently, retrospective single-center and multicenter studies have shown a decrease in in-hospital mortality associated with variceal hemorrhage over the past two decades. The decrease in mortality was largely due to the prevention of rebleeding with the use of earlier, more effective endoscopic therapy in combination with vasoactive medications and to the prevention of sepsis through the use of antibiotic prophylaxis. Despite this improvement, however, the mortality at 30 days among patients in Child–Pugh class C is still 32%, and 75% of the patients who require transjugular intrahepatic portosystemic shunt (TIPS) as rescue therapy to control index bleeding are in Child–Pugh class C. In addition, a Child–Pugh score above 9 has been identified as an independent risk factor for death, with a hazard ratio of 1.45 for each 1-point increase in the score.

Current practice guidelines for treating patients with acute variceal bleeding recommend fluid resuscitation, antibiotic prophylaxis, and vasoactive drugs such as glypressin or somatostatin analogs, followed by early endoscopy and either ligation or sclerosis of the varices. Despite these measures, failure to control index bleeding occurs in 10 to 20% of patients. An elevated hepatic venous pressure gradient (>20 mm Hg) measured within 24 hours after the start of bleeding is the best predictor of treatment failure. The use of TIPS to control variceal bleeding has largely been reserved for patients who require rescue therapy because hemostasis has not been achieved, either during the index bleeding or during the secondary-prophylaxis period. TIPS is extremely effective in controlling bleeding, with a reported rate of immediate hemostasis of 93% and with rebleeding in only 12% of patients. Nevertheless, mortality at 6 weeks among patients treated with rescue TIPS for uncontrolled index bleeding and rebleeding is very high (35%), reflecting the severity of their underlying liver disease as well as additional organ dysfunction that may have occurred owing to hypotension, infection, and aspiration.

In this issue of the Journal, García-Pagán and colleagues report the results of a randomized, multicenter study that compared early TIPS with optimal medical therapy (endoscopic therapy plus vasoactive drugs) in patients at high risk for rebleeding who were either in Child–Pugh class B with active bleeding at endoscopy or in Child–Pugh class C. After the acute bleeding, the medical-therapy group received endoscopic therapy until obliteration of the varices, followed by surveillance, beta-blockade (in 80% of patients), and nitrates (in 39% of patients). Thirty-one of the 32 patients randomly assigned to the early-TIPS group underwent shunting within 72 hours after endoscopy, and the portal-pressure gradient was reduced to less than 12 mm Hg in all but 2 of these 31 patients.

This study shows the benefit of early TIPS in patients with Child–Pugh class B or C disease who...
are at high risk for uncontrolled bleeding with standard therapy. Patients who were randomly assigned to receive TIPS had a significantly better chance of remaining free of bleeding than did those who received the standard care (97% vs. 50%), possibly owing to a greater reduction in portal pressure with TIPS than could be achieved with pharmacologic therapy.

The rate of survival at 6 weeks was 97% in the TIPS group as compared with 67% in the medical-therapy group, as a result of reductions in rebleeding, sepsis, and liver failure. However, the 86% 1-year survival rate in the TIPS group is somewhat surprising for patients with Child–Pugh class B or C disease who have variceal bleeding.

Does early TIPS alter the natural history of cirrhosis, or were these findings attributable to abstinence from alcohol in the large proportion of study patients with a diagnosis of alcohol-related cirrhosis (66%), half of whom were actively drinking at the time of presentation? Given that abstinence has been associated with improvement in liver function, it would be interesting to know whether any of these patients had improvement in the Model for End-Stage Liver Disease (MELD) score or the Child–Pugh class. An alternative theory is that the placement of TIPS early in the illness results in a large reduction in portal pressure and preservation of liver function, with a reduction in the risk of liver decompensation that has not typically been associated with the use of rescue TIPS.

Use of the newer stents, which are covered with extended polytetrafluoroethylene (e-PTFE), probably has an important bearing on the outcome of this study. For reasons that are unclear, e-PTFE-covered stents, as compared with bare-metal stents, are associated with better long-term survival among patients undergoing TIPS. This finding may be related to a reduced rate of TIPS dysfunction and thus fewer complications of portal hypertension with the newer stents, but there are no clearly established reasons for this phenomenon.

In conclusion, the study by García-Pagán and colleagues should stimulate a reevaluation of how we approach variceal bleeding in patients with Child–Pugh class B or C disease. Instead of taking a wait-and-see approach, physicians should consider the early use of TIPS with an e-PTFE-covered stent as first-line therapy rather than as rescue treatment if rebleeding occurs in high-risk patients with Child–Pugh B or C disease. Additional clinical trials of adequate size should be performed to confirm these findings and to examine the effect of a rapid reduction in portal pressure on disease progression in patients with cirrhosis of other causes.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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