Secondary Prophylaxis for Esophageal Variceal Bleeding

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KEYWORDS

- Secondary prophylaxis • Variceal rebleeding • β-blockers
- Endoscopic band ligation • Hemodynamic responders
- Transjugular intrahepatic portosystemic shunt (TIPS)

KEY POINTS

- A combination of drug treatment with β-blockers and endoscopic therapy with band ligation is the standard first-line option for secondary prophylaxis of variceal bleeding in cirrhosis. Transjugular intrahepatic portosystemic shunt is the recommended treatment when combination therapy fails.
- β-Blockers are the backbone of combination therapy, because their benefit goes beyond their portal-pressure-lowering effect and their efficacy extends to complications of portal hypertension other than bleeding. The added value of endoscopic band ligation is rather marginal.
- In the setting of rebleeding prevention, there is a lack of robust criteria to stratify patients according to their rebleeding risk, because some patients are likely to respond to β-blockers or endoscopic band ligation, whereas others present a high risk of rebleeding despite being on combination therapy.
- Hepatic venous pressure gradient monitoring can identify responders to β-blockers ("hemodynamic responders"), who have a very low rebleeding rate while treated only with β-blockers.
- Bleeders who could benefit more from a transjugular intrahepatic portosystemic shunt than from combination therapy include patients who first bleed while on β-blockers, those with contraindications to β-blockers or with refractory ascites, and patients with fundal varices.

Portal hypertension is responsible for one of the most severe consequences of cirrhosis, variceal bleeding. Patients with cirrhosis who survive an episode of variceal hemorrhage have a risk of rebleeding greater than 60% at 2 years[1]; this risk is higher

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during the first 6 weeks after the index bleeding. Because mortality related to each rebleeding episode is about 15% to 20%, interventions to prevent rebleeding are mandatory.

In this article, the currently recommended first-line treatment for the prevention of variceal rebleeding (secondary prophylaxis of variceal bleeding), combination of drugs (β-blockers) and endoscopic therapy (endoscopic band ligation, EBL) is critically revised. It is hypothesized that the efficacy of combination therapy mainly relies on β-blockers, whereas the additional benefit that EBL provides is rather marginal. Besides, a major limitation of current therapy is that it is uniformly recommended for the whole population of rebleeders, as robust clinical criteria are lacking to stratify patients according to their rebleeding risk while on combination therapy. A transjugular intrahepatic portosystemic shunt (TIPS), at present considered second-line treatment, could be a better choice to prevent rebleeding than standard therapy in those subgroups of patients at high risk of rebleeding if placed on combination therapy, or in those suffering from other complications of portal hypertension, such as recurrent or refractory ascites.

CURRENT RECOMMENDATIONS FOR THE PREVENTION OF ESOPHAGEAL VARICEAL REBLEEDING

- *β-Blockers and EBL reduce to a similar extent the rate of variceal rebleeding, but β-blockers reduce overall mortality, whereas EBL does not.*

β-Blockers and EBL are the 2 first-line therapies currently used to prevent variceal rebleeding. Both have comparable efficacy in the prevention of variceal rebleeding and bleeding-related mortality, but β-blockers reduce overall mortality, whereas EBL does not. This contention is supported by the results of the meta-analysis of the 8 trials (970 patients) that compared β-blockers plus nitrates and EBL in the prevention of variceal rebleeding. This meta-analysis showed that both treatments were similarly able to reduce upper gastrointestinal bleeding (relative risk [RR] 1.15; 95% confidence interval [CI] 0.81–1.63) and variceal rebleeding (RR 1.23; 95% CI 0.74–2.06) as well as bleeding-related mortality (RR 0.75; 95% CI 0.37–1.50), but overall mortality was only lowered with β-blockers (RR 0.78; 95% CI 0.64–0.96).[2,3] Another meta-analysis by Li and colleagues[4] found similar results.

The beneficial effect of β-blockers goes beyond the reduction in the variceal bleeding risk and is probably related to an improvement of other complications of portal hypertension. Indeed, patients in whom β-blockers achieve target reductions in hepatic venous pressure gradient (HVPG) show reduced rates of rebleeding, but also of spontaneous bacterial peritonitis and liver-related mortality.[5,6] Therefore, the observed reduction in mortality but not in rebleeding supports a nonhemodynamic effect of β-blockers in cirrhosis, which is independent of the portal pressure response and likely linked to reductions in porto-collateral blood flow and bacterial translocation.[7] This hypothesis is also supported by a meta-analysis of randomized trials and observational studies,[8] which showed that β-blockers reduce the risk of spontaneous bacterial peritonitis by 12%, independently of the hemodynamic response.

- *A combination of drug therapy, with β-blockers, and EBL is the recommended first-line therapy for the prevention of variceal rebleeding.*