Prevention of variceal rebleeding

Jaume Bosch, Juan Carlos García-Pagán

**Context** Variceal bleeding is the most frequent severe complication of portal hypertension and a leading cause of death and liver transplantation in patients with cirrhosis. Patients surviving a variceal bleed are at high risk of rebleeding (over 60% at 1 year). Portacaval shunts and transjugular intrahepatic portosystemic shunts (TIPS) are effective for prevention of rebleeding but carry a high risk of hepatic encephalopathy. Endoscopic techniques include band ligation (EBL) and injection sclerotherapy (EIS). Drug approaches are based on non-selective β blocker with or without isosorbide-5-mononitrate (ISMN).

**Starting point** David Patch and colleagues (Gastroenterology 2002; 123: 1013–19) randomised 102 patients surviving a variceal bleeding to EBL or drug therapy with propranolol with the addition of ISMN if target reductions in portal pressure (evaluated by the hepatic venous pressure-gradient [HVPG]) were not achieved at 3 months. Overall, results of drug therapy were similar to those of EBL (44% vs 54% rebleeding at 1 year). There were no differences in survival or non-bleeding complications. Christophe Bureau and colleagues (Hepatology 2002; 36: 1361–66) treated 34 patients with cirrhosis and portal hypertension with propranolol and measured HVPG after a median of 4 days. Target HVPG reductions were achieved in 13 “responders”. ISMN was added in the 21 “non-responders” and HVPG measured again; seven more patients achieved target HVPG reduction. Re-bleeding rates were lower in responders than in non-responders (10% vs 64%). Both studies suggest that drug therapy can be improved by adding ISMN to β blockers in those patients with an insufficient decrease in HVPG.

**Where next?** Long-term drug therapy is emerging as effective treatment for the prevention of variceal rebleeding. The role of HVPG monitoring as a guide to identifying patients requiring further treatment needs to be further evaluated. Trials to determine the best treatment for patients who do not respond to drug therapies are also required.

Patients with cirrhosis surviving a variceal bleed are at high risk of rebleeding (over 60% at 1 year), and mortality from each rebleeding episode is about 20%. Over the past two decades, several treatments (surgical, endoscopic, pharmacological) have been introduced which decrease the risk of rebleeding and mortality (table 1). However, differences in inclusion criteria and endpoint assessment preclude direct comparisons between studies.

**Treatment of portal hypertension**

In cirrhosis, portal hypertension is mainly due to increased resistance to portal blood-flow through the cirrhotic liver, and increased blood-flow in the portal and collateral circulation due to splanchnic vasodilatation and a hyperkinetic circulation. Portal hypertension can therefore be attenuated by decreasing intrahepatic resistance, reducing portal blood-flow, or both. Until recently, increased intrahepatic resistance could only be corrected by means of liver transplantation or portal-systemic shunts. Pharmacological approaches with drugs that act on increased hepatic vascular tone (see below) or on liver fibrogenesis (eg, interferon plus ribavirin in chronic hepatitis C infection) are alternatives.

Shunt surgery has been used for almost 50 years, and is based on the simple concept of bypassing the site of increased resistance. It is effective at decreasing the risk of variceal rebleeding, but has the disadvantage of enhancing encephalopathy and worsening liver failure. “Selective” shunts, such as the distal splenorenal shunt, or “calibrated” shunts, aim to reduce this problem. Interposition “C” or “H” graft mesocaval shunts are the more popular calibrated shunts, but experience in randomised trials is scarce. The transjugular intrahepatic portal-systemic shunt (TIPS) is a calibrated shunt with the advantage of not requiring surgery and carrying low mortality and morbidity from the procedure. However, long-term results and maintenance of TIPS are hampered by the frequent development of shunt dysfunction due to intimal proliferation within the stent shunt or hepatic vein outlet. The effectiveness of TIPS is similar to that for distal splenorenal shunts, but operative mortality is lower.

Local treatments act at the variceal bleeding site, without modifying the underlying pathophysiological abnormalities leading to haemorrhage. The best examples are endoscopic procedures (endoscopic injection sclerotherapy [EIS], endoscopic band ligation [EBL], and variceal obturation with bucrylate) and surgical techniques such as oesophageal transection or devascularisation. These procedures are often effective only for a short time, since portal pressure and blood-flow remain unchanged, and varices frequently recur (about 50% at 2 years). Strict endoscopic follow-up and repeated courses of therapy are required. However, these treatments are very useful in the management of the acute bleeding episode, where together with vasoactive drugs they are current recommended therapy.

EIS has been replaced by EBL, which is safer and more effective. Assessment of endoscopic treatments is difficult because, as in any interventional procedure, it is impossible to avoid observer bias and to have “blind” physicians. This
may partly explain the marked difference in efficacy noted in randomised trials depending on whether EBL was the experimental treatment or the control therapy. Reported rebleeding rates for EBL were better in trials that compared it with EIS than in more recent trials where it was the control arm against TIPS or drug therapy (IQR of rebleeding rates: 16–29% vs 38–56%).

Until recently, drug therapy was based on the use of vasoconstrictors that reduce portal pressure and blood-flow within the portal system. Non-selective β blockers (eg, propranolol, nadolol) act by this mechanism. Since increased vascular tone, partly due to reduced release of nitric oxide in the hepatic circulation, contributes significantly to increased hepatic resistance to portal flow in cirrhosis, it is rational to use vasodilators in the treatment of portal hypertension. Isosorbide-5-mononitrate (ISMN) is the only drug that has been tested in randomised trials. ISMN releases nitric oxide; unfortunately this occurs not only at the desired site—the hepatic vascular bed—but also in the systemic circulation, where it causes hypotension and may worsen sodium retention and renal function.

**Clinical-haemodynamic correlations**

Clinically significant portal hypertension is defined by a portal pressure-gradient (measured as hepatic venous pressure-gradient [HVPG]) above 12 mm Hg. Variceal bleeding rarely, if ever, occurs below this threshold (except in diseases that may be associated with a presinusoidal component, such as primary biliary cirrhosis, idiopathic portal hypertension, and schistosomiasis, in which HVPG may underestimate the portal pressure-gradient). Longitudinal haemodynamic studies have shown that if HVPG is decreased below this threshold, the patient has a lower risk of varical bleeding (table 2). Moreover, many studies show that if drug therapy achieves a reduction in HVPG of at least 20% of the baseline value, even without reaching values below 12 mm Hg, the residual risk of variceal bleeding is low, about 10% at 2 years. The only published randomised trial of EBL and drug therapy against EBL alone reported 2-year rebleeding of 23% in the combination group. However, this result is no better than the results in responders to drug therapy as defined by HVPG, and has the disadvantage of adding the cost and complications of the endoscopic treatment. Additional studies on this combined approach are required.

### Problems with drug therapy

Although it has been customary to adjust the dose of β blockers to achieve a 25% fall in the resting heart-rate, this reduction by no means guarantees an effective fall in HVPG, and there is no correlation between changes in heart rate and changes in HVPG. Our approach is to titrate up to the maximum tolerated dose, with dose escalation every 2 days. Doppler ultrasound is not useful in assessing response. Doppler ultrasound measures portal flow (especially in patients with liver disease. It is likely that other factors (eg, β-adrenoceptor polymorphisms) also modulate the response. Doppler ultrasound is not useful in assessing response to drug therapy and the only measurement that correlates with clinical response, other than HVPG, is endoscopic measurement of varical pressure. However, this measurement is more difficult than HVPG measurement, less reproducible, and cannot be considered as non-invasive.

Some non-responders will respond (on HVPG criteria) with the addition of a second drug. The addition of ISMN to a β blocker enhances the fall in portal pressure achieved by β blockade. About one-third of non-responders to β blockers become responders after addition of ISMN. Several randomised trials that compared the combination of a β blocker and ISMN with shunting, endoscopic therapy, or single drugs reported better results for rebleeding with the combination of a β blocker and ISMN.

Several studies have shown that the combination of EIS with drug therapy was better than either therapy alone. The only published randomised trial of EBL and drug therapy against EBL alone reported 2-year rebleeding of 23% in the combination group. However, this result is no better than the results in responders to drug therapy as defined by HVPG, and has the disadvantage of adding the cost and complications of the endoscopic treatment. Additional studies on this combined approach are required.

### Table 1: Reported rebleeding and mortality rates in randomised trials of different treatments to prevent variceal rebleeding

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number of studies</th>
<th>Number of patients</th>
<th>Reported rebleeding rates (IQR)</th>
<th>Reported mortality rates (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated</td>
<td>19</td>
<td>928</td>
<td>55–67%</td>
<td>23–54%</td>
</tr>
<tr>
<td>β blockers</td>
<td>26</td>
<td>983</td>
<td>37–57%</td>
<td>13–39%</td>
</tr>
<tr>
<td>EIS</td>
<td>54</td>
<td>2347</td>
<td>34–53%</td>
<td>18–36%</td>
</tr>
<tr>
<td>EIS+β blockers</td>
<td>13</td>
<td>445</td>
<td>19–49%</td>
<td>7–26%</td>
</tr>
<tr>
<td>EBL</td>
<td>18</td>
<td>836</td>
<td>20–43%</td>
<td>19–34%</td>
</tr>
<tr>
<td>TIPS</td>
<td>14</td>
<td>519</td>
<td>30–42%</td>
<td>12–32%</td>
</tr>
<tr>
<td>DRSR</td>
<td>9</td>
<td>309</td>
<td>12–22%</td>
<td>18–35%</td>
</tr>
<tr>
<td>DRS</td>
<td>309</td>
<td>11–31%</td>
<td>11–31%</td>
<td>22–55%</td>
</tr>
</tbody>
</table>

**DSRS**=distal splenorenal shunt. Table summarises results of studies using different treatment options included in several meta-analysis. Differences in inclusion criteria and outcome measurements preclude direct comparisons.

### Table 2: Risk of rebleeding in non-responders versus responders continued on drug therapy

<table>
<thead>
<tr>
<th>Reference</th>
<th>Number of patients</th>
<th>Drug</th>
<th>Non-responders *</th>
<th>Rebleeding rate in non-responders</th>
<th>Rebleeding rate in responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feu et al13</td>
<td>69</td>
<td>Propranolol</td>
<td>64%</td>
<td>54–5%</td>
<td>8%</td>
</tr>
<tr>
<td>Escorsell et al14</td>
<td>47</td>
<td>Propranolol</td>
<td>62%</td>
<td>44–8%</td>
<td>6%</td>
</tr>
<tr>
<td>Villanueva et al15</td>
<td>31</td>
<td>Nadolol+ISMN</td>
<td>55%</td>
<td>47%</td>
<td>7%</td>
</tr>
<tr>
<td>Villanueva et al16</td>
<td>49</td>
<td>Nadolol+ISMN</td>
<td>49%</td>
<td>66–6%</td>
<td>16%</td>
</tr>
<tr>
<td>Bureau et al17</td>
<td>34</td>
<td>Propranolol+ISMN</td>
<td>41%</td>
<td>64%</td>
<td>10%</td>
</tr>
<tr>
<td>Patch et al18</td>
<td>26</td>
<td>Propranolol+ISMN</td>
<td>45–63%</td>
<td>46–65%</td>
<td>7–13%</td>
</tr>
</tbody>
</table>

*Responders=proposal in HVPG of at least 20% of baseline values and/or below 12 mmHg.
combination than those previously reported with β blockers alone.15–17,22,23 (table 1). The combination was also more effective than β blocker alone in the only randomised trial to compare them directly.19 However, those who respond to β blockers alone do not benefit from the addition of nitrate and ISMN itself may cause unpleasant side-effects (headache, postural hypotension) and may facilitate sodium retention (although this has not been shown to occur in trials that used this drug combination).

Christophe Bureau and colleagues17 recommend adding ISMN to propranolol or nadolol in individual non-responders, but this requires measurement of the haemodynamic response in every patient. Assessment of HVPG response will provide strong prognostic information, since responders on HVPG criteria do better than non-responders (table 2). This assessment should be done early (preferably within 1–2 weeks of starting treatment) since David Patch and colleagues18 show that the risk of rebleeding is especially high during the first 6 weeks after the index haemorrhage. Others recommend adding ISMN in all patients, thus obviating the need to assess HVPG response.13,23,24 This idea seems reasonable in a high-risk situation, such as the prevention of recurrent bleeding.

The best treatment for a patient who does not respond to combined drug therapy is unknown. If drug therapy is continued, the risk of rebleeding is high (table 2). It has therefore been suggested that these patients be offered EBL. However, in the only study where this was done, the rebleeding rate was very high (88% at 2 years).17 The low rate of rebleeding with the combination of EBL and β blockers (albeit limited to only one randomised trial)19 suggests EBL with continuation of β-blocker therapy may be a reasonable approach. Clearly, further studies are needed to clarify this issue.

Pharmacological therapy is as effective as endoscopic treatment, and safer and less expensive (table 1).1 A pragmatic approach is therefore to start treatment with β blockers, except in patients with contraindications or who cannot tolerate them, and to add EBL in cases of bleeding while on β blockers (including patients who had their first bleeding episode while on prophylactic β blockers). ISMN can be added in all cases if HVPG measurements are not planned, or in those not responding to β blockers if the haemodynamic response is being evaluated. In the latter the second HVPG measurement should preferably be done within 2 weeks of starting therapy, to minimise the risk of rebleeding during this period. TIPS (and shunt surgery) should be used when drug and endoscopic treatments fail.

Conclusions

Drug therapy is a simple and safe way to prevent variceal rebleeding, provided target reductions in HVPG are achieved. Future steps forward include the development of non-invasive ways to assess the haemodynamic response so that therapy can be tailored not only in research studies, but also in clinical practice. However, this tailoring is not likely to be possible in the near future, and unless HVPG measurement is available, physicians will have to make decisions based on published results with a given treatment or combination (table 1). HVPG measurement is simple, safe, and easy, but if not done properly may confuse rather than help. If HVPG assessment is to be more generally used, hepatogastroenterologists will need to be trained in HVPG measurement, following well-defined guidelines and protocols. In the long term, it is hoped that more effective drugs or drug combinations will be available and that measuring the haemodynamic response will become unnecessary.

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References