Abstract

Patients surviving a first episode of variceal bleeding have a risk of over 60% of experiencing recurrent haemorrhages within 1 year from the index episode. Because of this, all patients surviving a variceal bleeding should receive active treatments for the prevention of rebleeding. β-Blockers ± isosorbide-5-mononitrate and band ligation are effective in preventing recurrent bleeding and both can be used. Combination of β-blockers ± isosorbide-5-mononitrate and band ligation may be the best treatment to prevent rebleeding but more studies are needed to confirm this issue. In patients with recurrent variceal bleeding despite appropriate medical and endoscopic treatment, transjugular intrahepatic porto-systemic shunt is highly effective in controlling bleeding. The efficacy is not significantly different from that of shunt surgery (distal splenorenal shunt or 8 mm H-graft shunt), especially since the introduction of polytetrafluoroethylene-covered stents. Therefore, in this situation, transjugular intrahepatic porto-systemic shunt using polytetrafluoroethylene stents should be the treatment of choice.

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Keywords: β-blockers; Endoscopic band ligation; Transjugular intrahepatic porto-systemic shunt; Variceal rebleeding

1. Pharmacological treatment

Pharmacological therapy is aimed at reducing portal pressure, which is the main pathophysiologic factor determining variceal bleeding. Portal pressure can be reduced either by reducing porto-collateral blood flow, or by reducing intrahepatic resistance, or both.

Non-selective β-blockers are the first line pharmacological therapy for the prevention of rebleeding [1]. They decrease portal pressure by decreasing porto-collateral blood-flow, through a blockade of cardiac β-1 receptors, leading to a decrease of cardiac output, and of vascular β-2 receptors, which induces splanchnic vasoconstriction.

Several meta-analyses have consistently found a marked benefit of β-blockers showing a reduction in rebleeding rate from 63% in controls to 42% in treated patients [2]. Notably, β-blockers also induce a significant decrease of overall mortality from 27% to 20% [2] and of mortality from bleeding [3]. According to the available data, the number needed to be treated (NNT) to prevent an episode of rebleeding by β-blockers is 5 and the NNT to avoid a death is 14 [2].

β-Blockers have been compared with endoscopic variceal sclerotherapy in the prevention of rebleeding. No significant differences were found either for rebleeding or for mortality but side effects were significantly less frequent and severe with β-blockers [2].

The combination of propranolol or nadolol plus isosorbide-5-mononitrate (IMN) enhances the reduction of portal pressure induced by non-selective β-blockers [4]. There are only two studies comparing IMN associated with propranolol [5] or nadolol [6] vs. the corresponding β-blocker alone, in the prevention of rebleeding. One of these studies showed significant benefit of the pharmacological associa-
Rebleeding

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Beta-blockers + IMN</th>
<th>EBL</th>
<th>OR 95% CI</th>
<th>OR 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Villanueva 2001</td>
<td>20/72</td>
<td>32/72</td>
<td>0.49 [0.24, 0.96]</td>
<td>2.37 [1.32, 4.26]</td>
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<tr>
<td>Lo 2002</td>
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<td>12/90</td>
<td>0.54 [0.22, 1.32]</td>
<td>1.30 [0.54, 2.95]</td>
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<tr>
<td>Patch 2002</td>
<td>11/44</td>
<td>18/47</td>
<td></td>
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</tr>
<tr>
<td>Romero 2005</td>
<td>21/67</td>
<td>17/52</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>234</td>
<td>231</td>
<td>0.98 [0.42, 2.26]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 78 (Beta-blockers + IMN), 79 (EBL).
Test for heterogeneity: C2 = 13.17, df = 3 (P = 0.006)
Test for overall effect: Z = 0.06 (P = 0.96)

Mortality

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Beta-blockers + IMN</th>
<th>EBL</th>
<th>OR 95% CI</th>
<th>OR 95% CI</th>
</tr>
</thead>
<tbody>
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<td>Villanueva 2001</td>
<td>23/72</td>
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<td>Lo 2002</td>
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<td>17/44</td>
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<td>Romero 2005</td>
<td>11/67</td>
<td>10/52</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>234</td>
<td>231</td>
<td>0.75 [0.50, 1.13]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 59 (Beta-blockers + IMN), 72 (EBL).
Test for heterogeneity: C2 = 2.42, df = 3 (P = 0.49)
Test for overall effect: Z = 1.37 (P = 0.17)

Fig. 1. Meta-analysis of the randomized clinical trial (RCTs) comparing β-blockers + isosorbide-5-mononitrate (IMN) with endoscopic band ligation of oesophageal variceal to prevent recurrent variceal bleeding and mortality. Squares indicate the odd ratio (OR) with the two treatments for each RCT. Horizontal bars denote the 95% confidence interval (CI) of the OR. The vertical line represents the line of identity of effect of the two treatments. The diamonds represent 95% CI of the pooled OR.

1.1. Hepatic venous pressure gradient (HVPG) guided therapy in the prevention of rebleeding

Pharmacological (or spontaneous) reduction of HVPG to <12 mmHg or by ≥20% of the baseline value (HVPG responders) virtually abolishes the risk of rebleeding and significantly reduces mortality [13] (Fig. 2). Achieving such a hemodynamic response is associated with a rebleeding risk that is even lower than that achieved using surgical shunts or TIPS [14]. As a consequence, in HVPG responders to add further treatment (i.e. band ligation) is unlikely to enhance efficacy but may increase side effects. On the other hand, it is still uncertain whether patients with an insufficient hemodynamic response to pharmacological therapy (non-responders) would benefit from alternative treatments. In the study by Bureau et al. [15], HVPG non-responders to β-blockers ± IMN were shifted to receive endoscopic band ligation. However, HVPG non-responders still have a extremely high rebleeding rate (87.5%). However, a small number of patients was included in the study. Preliminary data from a Spanish multicentre randomised clinical trial (RCT) comparing nadolol + IMN vs. nadolol + IMN + EBL [16] found no significant differences in rebleeding rates in HVPG non-responders treated with drugs alone or with drugs + EBL. All these available data suggest that EBL may not be the best alternative to reduce rebleeding in HVPG non-responders. It is therefore possible that we need more effective and aggressive therapies to reduce the high rebleeding tendency of HVPG non-responders (46–65% in a recent survey [14]). This was the idea of the study by Gonzalez et al in which a 19% rebleeding rate was observed in the HVPG non-responders that were treated with TIPS [17]. Unfortunately, the study included a low number of patients a no control group was incorporated. Thus, until more data is available HVPG guided therapy should only be used in the setting of clinical research.
2. Endoscopic treatment

Endoscopic treatment is a loco-regional treatment aimed at eradicating varices, and does not act on portal pressure. For this reason varices may recur after endoscopic treatment, and patients need to receive a life-long endoscopic follow-up to detect variceal recurrence.

Endoscopic injection sclerotherapy of oesophageal varices significantly reduces both the rebleeding and death risk. It takes 4–6 endoscopic sessions to eradicate varices, but recurrence of varices occurs in nearly 40% of patients within 1 year from eradication. This requires further endoscopic sessions to maintain eradication. The most serious side effects of therapy are dysphagia, oesophageal stenosis and bleeding from oesophageal ulcers, which may account for as much as 14% of all the rebleeding episodes. As commented above, sclerotherapy has no advantage over drug therapy and causes more frequent and severe side effects.

Endoscopic banding ligation has been proven superior to sclerotherapy [18]. Complications are significantly less frequent and severe with banding ligation, and therefore, banding ligation is the endoscopic treatment of choice [1]. Surprisingly, despite decreasing rebleeding rates, endoscopic ligation does not significantly improve survival compared with sclerotherapy. Although variceal eradication is achieved with a lower number of EBL sessions than with sclerotherapy, there is evidence that it is associated with higher recurrence of varices [18].

2.1. Combined endoscopic treatment

Sclerotherapy has been added (either simultaneously or after the reduction of variceal size to small) to endoscopic band ligation and compared to band ligation alone yielding contrasting results. The meta-analysis of these studies does not show any benefit either for rebleeding or for mortality, and importantly, it shows a trend towards an increasing complication rate with combination endoscopic therapy. Therefore, there is no rationale to combine both endoscopic approaches.

3. Combined endoscopic and pharmacological treatment

The association of injection sclerotherapy and β-blockers has been compared with either sclerotherapy or β-blockers alone. The meta-analysis of the RCTs comparing combination therapy with sclerotherapy alone showed a significant reduction of the rebleeding risk with combination therapy, but no differences for mortality [19]. Also when compared with β-blockers alone, combination therapy significantly reduced the rebleeding risk but without advantage for survival [2]. More recently, two RCTs have shown that adding β-blockers to the treatment of band ligation reduces the risk of rebleeding and variceal recurrence [20,21], suggesting that if EBL is used, it should be used in association with β-blockers.
More recently, a RCT, still published as an abstract [16], has evaluated whether EBL may improve the efficacy of the combined administration of nadolol + IMN. In this study, although adding band ligation to nadolol plus IMN was shown to be superior to nadolol + IMN alone in preventing variceal rebleeding, no significant differences were observed when considering rebleeding episodes of any cause. This was due to a greater number of ulcer-related bleeding in the treatment arm including banding. In addition, no difference in survival was observed.

Altogether these results emphasize that the combination of the best endoscopic treatment (EBL) and the best pharmacological treatment (β-blockers + IMN) may be the best choice, but this should be further evaluated.

4. Transjugular intrahepatic porto-systemic shunt (TIPS) and surgical shunts

TIPS has evolved as an means of decompressing portal system alternative to shunt surgery. TIPS has been compared with sclerotherapy and with banding ligation in several RCT to prevent variceal rebleeding [22]; the results of the majority of published studies show rebleeding rates of 9–23% for TIPS and of 21–66% for endoscopic treatment, demonstrating consistently that TIPS is superior to endoscopic therapy for the prevention of rebleeding.

Similarly, TIPS has also been shown to be superior to the combination of IMN and propranolol [23]. However, as expected, the very high effectiveness in preventing recurrent bleeding is associated with a marked increase in the risk of encephalopathy, and no benefit on survival. For these reasons, TIPS is regarded as a salvage therapy for those patients who bleed despite adequate medical and endoscopic treatment. Surgery is the other possible alternative to treat these patients.

TIPS has been compared with surgical shunts in two RCTs [24,25]. In the first it was compared with 8 mm portocaval H-graft shunt [24]. A significantly lower rebleeding rate was found with the surgical shunt. Significantly more patients required liver transplant in the TIPS group than in the surgical shunt group. There was no difference in mortality. The composite endpoint of “failures” which included rebleeding, shunt thrombosis, deaths, and need for transplant, was significantly higher for the TIPS. In the second trial TIPS was compared with the distal splenorenal shunt (DSRS) in Child’s class A and B patients [25]. No significant differences in rebleeding rate (5.5% in the DSRS group, and 9% in the TIPS group), incidence of hepatic encephalopathy, liver transplantation or mortality was found. These results were obtained with a significant higher reintervention rate in the TIPS group (82%), that was performed with bare stents, than in the DSRS group (11%). However, a multicentre RCT reported much lower obstruction and reintervention rates with the use of polytetrafluoroethylene (PTFE)-covered stents, that was associated with lower rates of recurrent bleeding or ascites without increased the incidence of encephalopathy, than with the use of bare stents [26]. These results suggest that the small disadvantage of TIPS vs. surgical shunt would be overcome by the use of PTFE-covered stents.

We recommend TIPS using PTFE stents as the treatment of choice for medical and endoscopic failure in patients with cirrhosis.

5. Prevention of rebleeding from portal hypertensive sources other than oesophageal varices

5.1. Gastric varices

The best treatment to prevent gastric variceal rebleeding is not well defined, since this condition has a low incidence. Type 1 gastric varices (GOV 1) are an extension of oesophageal varices along the lesser curvature of the stomach, and consequently, their management should be the same as for oesophageal varices. Very few data are available on the treatment of isolated gastric varices (IGV1) and fundal gastro-oesophageal varices (GOV 2). It is accepted that when IGV 1 are due to isolated splenic vein thrombosis splenectomy should be performed. In all other situations, evidence is poor. For acute bleeding from gastric varices, endoscopic variceal obturation (EVO) with N-butyl-cyanoacrylate, iso-butyrol-2-cyanoacrylate (bucrylate) or thrombin has been shown to be more effective than sclerotherapy or EBL both for the control of bleeding and for the prevention of rebleeding [27–29]. Therefore, these agents are preferred in the endoscopic therapy of fundal varices.

In clinical practice, non-selective β-blockers are usually added to EVO for the prevention of rebleeding.

Several papers demonstrated the effectiveness of TIPS in uncontrolled bleeding from gastric varices. In a recently published RCT [30], TIPS proved more effective than EVO in preventing rebleeding from gastric varices with similar survival and frequency of complications, despite the fact that TIPS stents were uncovered, and rebleeding rate after TIPS was much higher than previously reported, suggesting an inaccurate TIPS follow-up.

Recent AASLD practice guidelines[12] advise that PTFE-covered TIPS can be recommended for the prevention of the rebleeding from gastric varices in patients in whom bleeding recurs despite endoscopic and pharmacological therapy, even after a single failure has occurred.

5.2. Portal hypertensive gastropathy (PHG)

Prevention of recurrent bleeding from PHG should be based on non-selective β-blockers, at the same dosage as for treating oesophageal varices [31]. Adequate iron supplementation may be useful to prevent or correct chronic iron-deficient anaemia in patients with severe PHG [31]. Rare patients that have repeated severe bleeding from
PHG despite pharmacological therapy, may benefit from endoscopic ablation, either by argon plasma coagulation, neodymium:yttrium-aluminum-garnet (Nd:YAG) laser, or heater probe. If this is not feasible or fails, TIPS may be considered as an alternative therapy.

**Practice points**
- All patients surviving a bleeding episode should be treated to prevent rebleeding.
- $\beta$-Blockers $\pm$ IMN, band ligation or both should be used for prevention of recurrent bleeding.
- In patients who rebleed from oesophageal or gastric varices despite optimal medical and/or endoscopic secondary prophylaxis, TIPS using PTFE-covered stents is highly effective.

**Research agenda**
- Further evaluation of the role of the combination of $\beta$-blockers $\pm$ IMN plus EBL preventing variceal rebleeding.
- Identify patients with a high risk of medical and endoscopic treatment failure to evaluate the efficacy of applying more aggressive approaches (i.e. TIPS) before failure.
- Evaluate the role of targeting treatments according with baseline HVPG or its response to pharmacological treatments.

**Conflict of interest statement**
None declared.

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**References**


