Abstract

Up to 70% of the patients treated to prevent rebleeding will experience a bleeding episode within 2 years. The response should be adapted to the delay after the index bleed, the source and the severity of the haemorrhage, the underlying liver disease and the initial treatment to prevent rebleeding. Bleeding can be caused by endoscopic techniques themselves, which should incitate to complete obliteration rather than to switch to another therapy. Failure of drug therapy can be secondary to ineffectiveness, to a lack of compliance, or to an insufficient dosage. The two latter conditions may be corrected. Whenever a patient rebleeds in spite of optimal treatment, liver transplantation should be considered. When such a procedure is contra-indicated and in patients on the waiting list, a Transjugular intra-hepatic porto-systemic shunt (TIPS) should be performed.

Keywords: Band ligation; Beta-blockers; Digestive bleeding; Esophageal varices; Portal hypertension; TIPS

1. What is treatment failure in the prevention of variceal rebleeding?

After a first bleeding episode, approximately 20% of the patients will die [1], 17% will rebleed within 6 weeks and 70% within 2 years [2]. It is therefore mandatory to prevent rebleeding using β-blockers associated or not associated with nitrates and/or banding ligation. Nevertheless up to 50% of the patients treated will still experience rebleeding [3,4].

So far, the efficacy of treatments has never been assessed in the specific settings of failure in the prevention of rebleeding. We first have to define what failure of first line treatment is, then to address the issue of salvation techniques.

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of endoscopic treatment. Accordingly, it is usually considered that the occurrence of a bleeding episode before varices have been eradicated, should urge to complete obliteration by further sessions rather than to change therapy [16].

The failure of drug treatment can be accounted for by a lack of compliance, insufficient dosage or ineffectiveness of drugs. The last two conditions can be anticipated or corrected. Actually, several studies have shown that haemodynamic response to drugs is predictive of clinical efficacy. Whenever portal-portal gradient is decreased below 12 mmHg or by at least 20% of its baseline value, the rebleeding rate is below 10% [17–21]. When these PHG thresholds cannot be achieved with β-blockers alone, adding isosorbide mononitrate may increase the number of haemodynamic responders [21,22]. Assessing haemodynamic response to drugs therefore allows to predict clinical efficacy, to adapt the dosage or add a nitrates to recruit responders and to identify a sub-group of non-responders who should be offered another treatment.

Finally, optimal first line therapy to prevent variceal rebleeding is either drug therapy tailored according to haemodynamic response, or the association of β-blockers and band ligation. The failure of such optimal therapy should be considered an indication for a new treatment.

2. What should be done after the failure of optimal first line treatments

The efficacy of treatments after failure of variceal rebleeding prevention has never been specifically assessed by randomized controlled studies. The difference between “first line” and “second line” treatments lies on studies including “first line” patients. Are usually considered second-line treatments therapeutic techniques which are more effective in preventing rebleeding than drugs and/or band ligation, but do not improve survival and have more frequent or more severe side effects.

Whenever possible, liver transplantation should be considered in patients whose liver function is usually poor. When it is contra-indicated and in patients on the waiting list, or the few whose liver function is fairly preserved, a shunting procedure should be considered. Fourteen studies compared TIPS to other treatments aiming to prevent rebleeding in portal hypertensive patients: sclerotherapy [23–28], band ligation [29–31], endoscopic treatment plus β-blocker [32–35] and β-blocker plus nitrate [36]. As a whole, meta-analyses [37–39], showed TIPS to be more effective in preventing rebleeding, reducing the risk by approximately 50% (Table 2). But the incidence of encephalopathy was significantly greater in patients treated with TIPS and survival was not changed. It is to be noticed that patients treated with TIPS had to be switched to another treatment in only 2% of the cases, as compared to 16% in the other groups. This supports the efficacy of TIPS as a “second line treatment”.

TIPS has also been compared to shunt surgery: 8 mm H graft portacaval shunts [40] and distal splenorenal shunt [41]. The main results of these studies are reported in Table 3. As demonstrated by these trials, the main drawback of TIPS is a high rate of occlusion: up to 80% in 2 years. It is therefore mandatory to monitor the patency of TIPS over time and if dysfunction is suspected, angiography and angioplasty whenever needed, should be performed. Two main mechanisms can lead to shunt narrowing or obstruction. The first one is thrombosis which is observed in approximately 10% of the patients, almost exclusively during the first month after TIPS insertion. The second mechanism, by far the most frequent, is overproliferation of the pseudo-intima which covers the intra-parenchymal tract of the prosthesis in the liver within a mean of 3 weeks [42]. These obstructions can now be prevented using covered prostheses. With polytetrafluoroethylene (PTFE) covered stents, an international multicentre randomized trial reported a 12% obstruction rate in 1 year (Fig. 1), without increased incidence of encephalopathy, probably because the risk inherent to blood shunting was overcome by a significantly smaller rate of clinical relapses and need for TIPS refection [43]. This effective prevention of shunt obstruction was maintained over time [44]. Another concern was the cost-effectiveness of TIPS as compared to banding ligation [45]. However, a modelling approach found TIPS to

### Table 1

Definitions according to Baveno IV consensus workshop [7–9]

1. Failure of secondary prophylaxis:
   - Occurrence of the first clinically significant rebleeding episode related to portal hypertension

2. Clinically significant rebleeding:
   - Haematemesis or melaena with a transfusion requirement of an ABRI > 0.5 and/or decrease of 3 g/dl of haemoglobin (9% haematocrit) if no blood transfusion is given.

3. Adjusted Blood Requirement Index (ABRI):
   - $\text{ABRI} = \frac{\text{BU}}{[(\text{final Hct} - \text{initial Hct}) + 0.01]}$
   - BU = blood unit
   - Hct = haematocrit
   - 0.01 = constant introduced to discard impossible calculations due to null denominator

### Table 2

Comparison of TIPS and endoscopic treatment (ET)

<table>
<thead>
<tr>
<th>First author</th>
<th>Number of patients</th>
<th>Rebleeding</th>
<th>Encephalopathy</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>ET (%)</td>
<td>TIPS (%)</td>
<td>ET (%)</td>
</tr>
<tr>
<td>Papatheodoridis V</td>
<td>811</td>
<td>47</td>
<td>19</td>
<td>19</td>
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<tr>
<td>Luca A</td>
<td>750</td>
<td>52</td>
<td>21</td>
<td>19</td>
</tr>
<tr>
<td>Burroughs AK</td>
<td>948</td>
<td>43</td>
<td>19</td>
<td>19</td>
</tr>
</tbody>
</table>

Main results of three meta-analyses [37–39].
Table 3
Main results of studies comparing TIPS to 8 mm H graft portacaval shunt and to distal splenorenal shunt (DSRS)

<table>
<thead>
<tr>
<th></th>
<th>Rebleeding</th>
<th>Reinterventions</th>
<th>Encephalopathy</th>
<th>Survival a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosemurgy et al. [40]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H graft</td>
<td>7.6%</td>
<td>p &lt; 0.01</td>
<td>11%</td>
<td>3% NS</td>
</tr>
<tr>
<td>TIPS</td>
<td>30%</td>
<td></td>
<td>48%</td>
<td>4.5% NS</td>
</tr>
<tr>
<td>Henderson et al. [41]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DSRS</td>
<td>5.5%</td>
<td>NS</td>
<td>11%</td>
<td>50% NS</td>
</tr>
<tr>
<td>TIPS</td>
<td>10.5%</td>
<td></td>
<td>82%</td>
<td>50% NS</td>
</tr>
</tbody>
</table>

a Survival: actuarial rates at 10 years in Rosemurgy et al.’s trial, at 5 years in the Henderson et al.’s study.

Fig. 1. Probability of remaining free of shunt dysfunction after TIPS with a bare prosthesis (—) or a PTFE covered stent (…) from Bureau et al. [43]. Figures below the graph indicate the number of patients at risk (bare stents: first line).

be in the same time more effective and more cost-effective than banding ligation [46]. These results were recently confirmed by a multicentre study performed in the US [47], which showed that TIPS was actually as effective as distal splenorenal shunt in preventing rebleeding while the use of coated stents TIPS proved more cost-effective.

TIPS should be preferred to surgery also because it does not hamper the chance for transplantation, it avoids the complications of laparotomy, and it can be reduced in diameter or occluded if needed by the occurrence of refractory hepatic encephalopathy.

3. In conclusion

Variceal rebleeding should not be systematically considered a treatment failure. The need for an alternative therapy will be decided according to the severity of the haemorrhage and of the underlying liver disease, the general status of the patient, the delay since the first bleeding episode . . . . Drug therapy might be optimized by measuring haemodynamic response to tailor the dosage and/or add nitrates to β-blockers. The association of band ligation to drug therapy should also be considered. If optimal “first line” therapy has failed, the patient should be treated by TIPS using PTFE covered prostheses and considered for liver transplantation whenever possible.

Practice points

- Any patient who has bled from ruptured oesophageal or gastric varices should be given a treatment to prevent rebleeding.
- If first line treatments fail, a TIPS should be performed whenever possible.
- Liver transplantation should be considered in these patients.

Research agenda

- Non-invasive means to assess the efficacy of drugs should be found.
- Post-TIPS encephalopathy should be prevented by new treatments or a better selection of the patients.
- The place of TIPS as first line treatment in patients with a high rebleeding risk should be evaluated.

Conflict of interest statement
None declared.

References


