Prevention of recurrent variceal bleeding. Endoscopic and pharmacologic treatment

R. de Franchis, Alessandra Dell’Era, Linda Fazzini, Stefania Zatelli, M. Primignani

SUMMARY

Bleeding from esophageal and gastric varices is the most severe complication of portal hypertension. The long-term probability of rebleeding of patients surviving a variceal bleed is about 60%, with a mean risk of death of about 45%. Thus, all patients who survive an episode of variceal bleeding must be treated to prevent rebleeding. Pharmacological therapy with beta-blockers has been shown to reduce the rebleeding rate by about 40%. Endoscopic methods such as sclerotherapy and rubber band ligation have also been shown to be effective in reducing the incidence of variceal rebleeding. Banding was markedly superior to sclerotherapy in preventing rebleeding, while mortality was similar with either treatment. The advantage of combining sclerotherapy with beta-blockers appears to be small. The value of combining banding and sclerotherapy with the aim of reducing variceal recurrence is still unproven. In conclusion, the first line treatment for prevention of recurrent variceal haemorrhage is either β-blockade or band ligation. In patients who have a contraindication to β-blockers therapy or who have bled while on β-blockers, band ligation is the preferred treatment to prevent recurrent variceal hemorrhage.

Key Words: Portal hypertension, Variceal haemorrhage, beta-blockers, sclerotherapy; endoscopic banding ligation, meta-analysis

INTRODUCTION

Gastrointestinal bleeding is the most severe complication of portal hypertension. Although cirrhotic patients may bleed from a variety of portal-hypertension related causes (i.e. portal hypertensive gastropathy, colopathy, hemorrhoids and rectal varices), esophageal and gastric varices are by far the most common sources of bleeding in these patients.

If a patient survives an episode of variceal bleeding, he has a high probability of rebleeding.

Rebleeding can be conventionally divided into two phases: early (within 6 weeks of the bleeding episode), and late (after 6 weeks). The reported incidence of early rebleeding ranges between 30 and 40% within the first six weeks. The risk is maximal in the first 5 days, then declines slowly over the first 6 weeks, and becomes virtually equal to that before bleeding after the sixth week.

In a recent Italian survey, rebleeding within 6 weeks occurred in 37 of 199 patients (18.6%), with 40.5% of rebleeds occurring in the first 5 days. Early rebleeding is significantly associated with the risk of death within 6 weeks. This suggests that its prevention should be a primary objective of therapy of the acute bleeding episode.

Data on long-term rebleeding can be obtained by analyzing the control groups of 21 randomized controlled trials carried out between 1982 and 1991, in which pharmacologic treatment with beta-blockers or endoscopic sclerotherapy were compared with placebo or non active treatment for prevention of rebleeding. The incidence of rebleeding ranged between 32% and 84%, with a mean of 59%. (Figure 1). Long-term mortality in these patients ranged between 4% and 78%, with a mean of 46% (Figure 1). Because of these dismal figures, the general consensus is that all patients who survive an episode of variceal bleeding must receive some effective...
form of treatment to prevent rebleeding.

In this paper we will review the available pharmacologic and endoscopic treatments to prevent rebleeding.

**Beta blockade versus placebo**

Eleven randomized controlled trials compared beta-blockers with placebo.\textsuperscript{5,7,11,15,17,19,23} Meta-analysis (Figure 2) showed a highly significant reduction of rebleeding in patients receiving beta-blockers,\textsuperscript{26} while the reduction in mortality rates with beta-blockers just missed statistical significance.\textsuperscript{26}

**Long-term sclerotherapy vs. conservative measures**

Sclerotherapy has been compared with conservative measures\textsuperscript{4,6,12,14,18,20,22,24} in 10 trials including a total of 1259 patients (Table 1). Meta-analysis showed a significant reduction of rebleeding in sclerotherapy-treated patients (P.O.R. 0.57; 95% C.I. 0.45-0.71) (Table 1, Figure 2). Mortality was also significantly reduced (P.O.R. 0.72; 95% C.I. 0.57-0.90) (Figure 2). It is noteworthy that the complication rate was higher in patients treated by sclerotherapy in all trials.

**Sclerotherapy vs long-term beta-blockers**

Nine trials\textsuperscript{18,27-34} with a total of 752 patients compared...
sclerotherapy with long-term beta-blockers (Table 2). In this group of trials meta-analysis showed a significant reduction of rebleeding in favor of sclerotherapy (P.O.R. 0.64; 95% C.I.: 0.48-0.85, Table 2, Figure 2). However, an important qualitative heterogeneity between trials results has been shown₂⁶ which approaches significance (P = 0.07), and weakens the results of meta-analysis, suggesting that the advantage of sclerotherapy may be small. None of the trials showed a significant difference in mortality in either direction, and this is reflected in the meta-analysis (P.O.R. 0.82; 95% C.I. 0.60-1.11).

**Sclerotherapy vs sclerotherapy + b-blockers**

In 10 trials, 35-44 involving 600 patients (Table 3) sclerotherapy was compared with a combined treatment of sclerotherapy plus beta-blockers. In these trials, the combined treatment was significantly better than sclerotherapy alone in preventing rebleeding (P.O.R. 0.65; 95% C.I. 0.46-0.92), but qualitative heterogeneity in trials results was found, ²⁶ and thus meta-analysis should be interpreted with caution. Mortality was similar with the two treatment regimes (P.O.R. 0.81, 95% C.I. 0.50-1.29, Table 3, Figure 2).

**Sclerotherapy vs. sclerotherapy + subcutaneous octreotide**

In three trials, 45-47 sclerotherapy was compared with sclerotherapy plus subcutaneous octreotide. These trials differed greatly in study design, dosage and time of octreotide administration, and gave contrasting results. In the first one, 58 patients were randomized after bleeding control to receive sclerotherapy alone (32 patients.) or plus subcutaneous octreotide, 100µg t.i.d. for one month (26 patients.). The rebleeding rate throughout three months of follow-up was not significantly different in the two treatment groups (34% vs. 31%, p = 0.73). Ninety-day mortality was also similar in the two groups (22% vs. 38%; p = 0.16). In the second trial ⁴⁶ 32 patients were enrolled three weeks after a variceal bleeding episode which had been controlled with two sessions of sclerotherapy. The patients (16 in each group) were randomized to sclerotherapy every three weeks, alone or plus octreotide (50 µg b. i. d. for 6 months). Rebleeding (6% and 44% respectively, p = 0.037) and mortality (0% and 25% respectively, p < 0.02) were both significantly better in patients receiving the combined treatment. The study was not double-blind and there was no check for compliance in the administration of octreotide. The 44% rebleeding rate in patients treated with sclerotherapy alone is exceedingly high, since patients were enrolled three weeks after the index bleed and after two sessions of sclerotherapy, when the rebleeding risk is markedly decreased. This raises the question of a severe selection bias. The third study ⁴⁷ had a complex design. After bleeding control, patients were randomized to octreotide (100 µg t.i.d. for 15 days) or placebo (131 patients for each group). Patients were stratified according to whether they were eligible or not for long-term treatment according to clinical criteria. Those eligible could receive beta-blockers, sclerotherapy or both. As a result, only 23 patients were randomized to sclerotherapy (± nadolol) plus octreotide, and 28 to sclerotherapy (± nadolol) plus placebo. The six-week rebleeding rate was 25% in the former group, and 70% in the latter (p = 0.02). Again, the extremely high rebleeding rate in patients treated with sclerotherapy alone raises the doubt of selection bias. From the results of these 3 studies, the clinical efficacy of subcutaneous octreotide in reducing early rebleeding in pa-

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**Table 2.** Randomized controlled trials of treatments for the prevention of variceal rebleeding-II

<table>
<thead>
<tr>
<th>Author</th>
<th>Yr.</th>
<th>Ref. N°</th>
<th>Treatment</th>
<th>N° Pts.</th>
<th>% Rebleeding</th>
<th>% Mortality</th>
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<td>Fleig</td>
<td>1988</td>
<td>64</td>
<td>Sc/β</td>
<td>36/34</td>
<td>28/29</td>
<td>8/15</td>
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<td>TersØ</td>
<td>1993</td>
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<td>59/57</td>
<td>34/51</td>
<td>30/21</td>
</tr>
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<td>Alexandrino</td>
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<td>66</td>
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<td>31/34</td>
<td>55/74</td>
<td>29/32</td>
</tr>
<tr>
<td>Dollet</td>
<td>1988</td>
<td>67</td>
<td>Sc/β</td>
<td>28/27</td>
<td>64/44</td>
<td>54/44</td>
</tr>
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<td>Westaby</td>
<td>1990</td>
<td>68</td>
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<td>56/52</td>
<td>45/54</td>
<td>38/42</td>
</tr>
<tr>
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<td>28/38</td>
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<td>23/26</td>
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<td>Martin</td>
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P.O.R. (95% C.I.) 0.64 (0.48-0.85) 0.82 (0.60-1.11)
Table 3. Randomized controlled trials of treatments for the prevention of variceal rebleeding - III

<table>
<thead>
<tr>
<th>Author</th>
<th>Yr.</th>
<th>Ref. N°</th>
<th>Treatment</th>
<th>N° Pts.</th>
<th>%Rebleeding</th>
<th>%Mortality</th>
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<tr>
<td>Sclerotherapy (Sc) vs β-Blockers + sclerotherapy (SP or SN)</td>
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<td>72</td>
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<td>27/30</td>
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<td>15/16</td>
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<td>19/22</td>
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<td>14/14</td>
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<td>39/35</td>
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<td>58/56</td>
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<td>Avgerinos</td>
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<td>79</td>
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<td>Villanueva ¶</td>
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<tr>
<td>P.O.R. (95% C.I.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.65 (0.46-.92)</td>
<td>0.81 (050-1.29)</td>
</tr>
</tbody>
</table>

SP = Sclerotherapy + propranolol
SN = Sclerotherapy + nadolol

Patients undergoing sclerotherapy remains uncertain.

**Long-term endoscopic therapy vs. long-term beta-blockers + nitrates**

Two recent trials by the same group of investigators have compared sclerotherapy with a oral medical treatment consisting of nadolol plus isosorbide-5-mononitrate48,49 (Figure 3). In the first study,48 eleven of 43 (25.6%) patients on the medical regimen rebled, compared with 23 of 43 (53.5%) treated by sclerotherapy (P < 0.001). The rebleeding rate of medically treated patients in this study is the lowest ever reported in trials of medical prevention of variceal rebleeding, while that of patients in the sclerotherapy arm is among the highest reported for this kind of treatment. The corresponding figures for mortality were 9.3% and 20.9% (P = 0.07). In the second trial,49 139 patients were randomized to receive either band ligation (70 patients) or nadolol plus isosorbide-5-mononitrate (69 patients.). During a mean follow-up of 20 months, 35 patients (50%) in the band ligation group and 24 patients (38%) in the medical treatment group rebled (p = NS). Mortality was 39% and 32% respectively (p = NS). If the results of these studies are confirmed, the combination of beta-blockers + nitrates is likely to become the first-choice medical therapy to prevent variceal rebleeding, and the standard with which alternative therapies should be compared.

**Long-term sclerotherapy vs. long-term rubber band ligation**

Fourteen trials50-63 with a total of 1181 patients have compared long-term sclerotherapy with long-term rubber band ligation (Table 4). Ligation was better than sclerotherapy in preventing rebleeding in all studies, and was significantly so in 5,52,54,55,57,62,63 Meta-analysis shows a strong benefit for rubber banding (P.O.R. 0.45, 95% C.I. 0.35 - 0.59, Table 4, Figure 2). Only 11 trials give figures for mortality: in 2 rubber banding was significantly better than sclerotherapy51,54 while the other studies showed small, not significant changes in either direction. Meta-analysis confirms that the two treatments are equivalent (P.O.R. 0.84; 95% C.I. 0.62-1.15).
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Table 4. Randomized controlled trials of treatments for the prevention of variceal rebleeding-IV

<table>
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<tr>
<th>Author</th>
<th>Yr.</th>
<th>Ref.</th>
<th>Treatment</th>
<th>N° Pts.</th>
<th>% Rebleeding</th>
<th>% Mortality</th>
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<td>Stiegmann</td>
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<td>13/10</td>
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<td>Fakhry * ¶</td>
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P.O.R. (95% C.I.)
0.45 (0.35-0.59) 0.84 (0.62-1.15)

Symbols and abbreviations used in tables and figures:
¶ = published in abstract form, * = study containing patients with schistosomiasis, P.R.D. = pooled rate difference
P.O.R. = pooled odds ratio, 95% C.I. = 95% confidence intervals

The strong difference in rebleeding rate in favor of rubber banding is probably the consequence of several factors: the number of treatment sessions required to achieve variceal eradication was significantly smaller with banding (2.5 to 4.1 sessions) than with sclerotherapy (2.9 to 6.5 sessions) in all but one of the 12 trials reporting this data. In most studies, this corresponded to a shorter time to achieve eradication: decreasing such time reduces the ‘vulnerable phase’ of endoscopic treatment, (i.e. the time when the risk of rebleeding is decreased but still exists, owing to the incomplete eradication of varices). In addition, the number of clinically significant complications was generally lower in patients treated with banding: esophageal stenosis after banding was reported in only one trial (2%), while its incidence after sclerotherapy ranged between 0 and 33%; the incidence of bleeding from treatment-induced ulcers was lower with banding in all studies but two. Finally, the incidence of septic complications (pulmonary infections, spontaneous bacterial peritonitis) and of fatal complications was also lower in patients undergoing rubber band ligation, although the difference with sclerotherapy was small.

In view of these results, rubber band ligation has become the endoscopic treatment of choice for the prevention of recurrent bleeding from esophageal varices.

Figure 4. Meta-analysis of randomized controlled trials for prevention of variceal rebleeding: Sclerotherapy (EVS) vs. Rubber Band Ligation (EVL): Recurrence of varices (7 trials; 673 patients).

It is unclear whether banding ligation is followed by a higher rate of variceal recurrence in comparison with sclerotherapy. Of the 8 trials that give the information, variceal recurrence was slightly more frequent after sclerotherapy than banding in three, and more frequent...
after banding in 5, 55-56, 61, 63 with a difference reaching statistical significance in 3, 57, 61, 63. In the eight studies, recurrences ranged between 8% and 92% after banding, and between 2% and 55% after sclerotherapy. Interpretation of these results is made difficult by the different lengths of follow-up in the studies, and by differences in the definitions of variceal recurrence. Meta-analysis shows no significant difference between treatments (P.O.R. 1.31; 95% C.I. 0.89-1.94) (Figure 4). At any rate, in recent years several combinations of treatments have been proposed to reduce the recurrence rate of varices following band ligation. In two studies, banding was compared with a regimen consisting of band ligation plus simultaneous sclerotherapy.67-68 The combined treatment was superior to banding alone in one and showed no advantage in the other.68 In another study, banding was compared with a sequential therapy with initial banding followed by low-dose sclerotherapy after varices were reduced to small residual cords.69 The combined treatment significantly reduced both variceal recurrence and rebleeding. In a further study, a comparison was made between banding alone and banding followed by microwave coagulation of the lower esophagus, leading to mucosal fibrosis.70 Variceal recurrence was observed in 15/25 (60%) of patients treated with banding alone, and in 4/25 (16%) of those treated with the combined regimen (p=0.03). In conclusion, it is still unclear whether variceal recurrence is more frequent after banding than after sclerotherapy. The clinical value of combined treatments to reduce variceal recurrence rates after banding is unknown.

**CONCLUSIONS**

The first line treatment for prevention of recurrent variceal hemorrhage is either β-blockade or band ligation.65 In patients who have a contraindication to β-blocker therapy or who have bled while on β-blockers, band ligation is the preferred treatment to prevent recurrent variceal hemorrhage.65

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