The role of endoscopic therapy in the treatment of bleeding varices

Sabine Bohnacker MD
Assistant

Parupudi V. J. Sriram MD
Assistant

Nib Soehendra MD
Director
Department of Interdisciplinary Endoscopy, University Hospital Eppendorf, Hamburg, Germany

The role of endoscopy in bleeding varices is both diagnostic and therapeutic. While sclerotherapy of oesophageal varices remains an established modality, ligation has, in view of its higher safety margin, turned out to be superior in recent years. The excellent initial results of ligation are, however, tainted by a higher recurrence rate in the long term. Since the end-point of treatment is the achievement and maintenance of variceal eradication, the addition of low-dose sclerotherapy following initial eradication by ligation seems to be the optimal method to combine the best of both techniques. In the management of life-threatening bleeding from oesophageal varices and gastric varices, cyanoacrylate remains the only promising non-surgical option. Primary endoscopic prophylaxis is still under evaluation. It is only justified in high-risk patients with large varices bearing red colour signs and in the presence of an intolerance of or contra-indication to propranolol. When indicated, ligation seems to be preferable, and the addition of low-dose sclerotherapy after initial variceal eradication may maintain the benefits accrued in such high-risk patients. The present review examines the available evidence regarding the above issues in the recent literature.

Key words: varices; bleeding; endoscopy; therapy.
haemorrhage is associated with a mortality of 25–40%, and mortality resulting from re-bleeding in the first year following the index bleed is as high as 50%. These facts need to be kept in mind while managing patients with varices.

Despite the availability of several modalities of treatment [endoscopic therapy, pharmacological therapy, balloon tamponade, shunt surgery and transjugular intrahepatic portosystemic shunt (TIPS)], bleeding from varices continues to be the leading cause of death in patients with portal hypertension. The role of endoscopy in the management of oesophagogastric varices depends on the clinical stage at which the patient is encountered. Depending on the history of active, inactive or no bleeding, endoscopic management can be emergency, elective or prophylactic. The ultimate outcome depends on several factors, including the presence of complications, for example re-bleeding and infection, the degree of hepatic function, the magnitude of the first bleed and any associated co-morbidity. Patients, especially those suffering from advanced cirrhosis, have limited functional hepatic reserve to cope with the complications of delayed or inadequate haemostasis.

**ENDOSCOPY IN VARICEAL BLEEDING**

**Source of bleeding**

In patients presenting with gastrointestinal bleeding, the primary role of endoscopy is to establish the source of bleeding, irrespective of the past history, and to attempt to control the bleeding endoscopically. About one-third of patients with a known history of portal hypertension can have bleeding from a non-variceal source such as a Mallory–Weiss tear, gastroduodenal erosion or ulcer. In such patients, the use of balloon tamponade as a temporizing measure before endoscopy is futile and can be potentially fatal, for example by aggravating oesophageal tears.

The use of pharmacological methods is thus preferable to balloon tamponade. It may be very helpful if the patient needs to be transported or when the haemodynamic status does not allow immediate endoscopy. Both somatostatin and octreotide have shown an efficacy similar to that of endoscopic sclerotherapy alone in the control of acute variceal bleeding. In a remarkable prospective, double blind, randomized study, Levacher et al used drug treatment (terlipressin), followed by endoscopy, in 76 cirrhotos with active bleeding ‘in the field’. Control of bleeding and survival were significantly better in the terlipressin group compared with the placebo group, with no serious side-effects. Balloon tamponade should be restricted to situations in which emergency endoscopy cannot be performed and pharmacotherapy fails or is unavailable.

**Resuscitation and general measures**

Acute bleeding requires the haemodynamic stabilization of the patient. For the most efficient management of this complex emergency, as well as for the optimum safety of the patient, the presence of an anaesthetist is advisable. A secure venous access, preferably a central venous line, is mandatory to guide fluid replacement. The early replacement of blood loss is essential; however, unmonitored transfusions may raise the portal pressure, inducing recurrent bleeding. In the presence of coagulopathy caused by liver dysfunction, fresh frozen plasma supplements may be required.

During active bleeding associated with haematemesis, the importance of airway management cannot be overstressed. Endotracheal intubation should be considered
early. This prevents the aspiration of blood and oropharyngeal secretions, and allows for better monitoring and control of patients’ respiratory situation, thus facilitating emergency endoscopy.

Sedation
For emergency endoscopy, sedation should be avoided, especially in cirrhotics with poor liver function and pre-coma. If the patient is too agitated, short-acting agents such as propofol are preferable. If benzodiazepine derivatives are used, the antagonist flumazenil should be available.

Equipment
For any successful procedure, the availability of the appropriate equipment and accessories is equally important as knowledge and skill. A therapeutic endoscope with a working channel of at least 3.2 mm is optimal to allow for adequate suction beside the accessories. An additional suction pump is mandatory for clearing oropharyngeal secretions and refluxed gastric contents during the procedure. In presence of a large quantity of blood and clots in the stomach obscuring the view, a 6 mm channel endoscope can rapidly clear the stomach. Evacuating the blood from the stomach not only allows for better vision, but may also help in reducing the subsequent risk of hepatic encephalopathy in cirrhotics with liver dysfunction. In cases of blood or food material sticking to the mucosa, a water pump connected to the jet channel of the endoscope can be of immense help in identifying the source of bleeding or any persisting bleeding after treatment.

ENDOSCOPIC HAEMOSTASIS OF OESOPHAGEAL VARICEAL BLEEDING
Of all the available methods, endoscopic treatment is generally preferred because of its efficacy, lower morbidity and lower mortality. Technically, the available options are injection sclerotherapy (EST), the use of mechanical ligation devices such as bands (EVL), loops, snares and clips, and variceal obliteration using the tissue glue Histoacryl. Injection and mechanical methods result in thrombosis of the treated varix and cause an ischaemic necrosis and ulceration of the overlying mucosa, which heals by fibrosis. In contrast, obliteration by glue injection permanently occludes the varix without inducing extensive inflammation or fibrosis. The relative merits and demerits of the techniques depend on factors inherent to the method, the material, the technique and the skill of the performer.

Active variceal bleeding
Sclerotherapy or ligation?
Sclerotherapy remains the most popular and widely used method for controlling actively bleeding varices, since it is effective, inexpensive, widely available and time-tested, and can be performed even when the site of bleeding on the varix is not clearly visualized. There are, however, several drawbacks to using EST in cases of active bleeding. Injecting large amounts of sclerosant or repeating sclerotherapy within a
short interval leads to excessive tissue necrosis, further bleeding and an increased risk of oesophageal perforation.

On the other hand, some consider variceal ligation to be cumbersome in the setting of active bleeding. The instrument initially has to be withdrawn after diagnostic endoscopy in order to load the apparatus. The ligation device attached to the tip of the endoscope can restrict the field of vision, especially when blood clots lodge in the cap, and it may be difficult to locate the bleeding point because of the reduced vision. However, several studies on ligation have included patients with active bleeding and have not reported any special difficulty. The exact localization and ligation of the bleeding point is not essential, and placing bands near the gastro-oesophageal junction reduces the flow and facilitates further banding. With the use of multiband ligators, the field of view increases as the bands are deployed, and flushing the working channel of the endoscope is possible while the device is in situ. In the recent modification of multiligators, the length of the distal transparent cap is extended beyond the position of the rubber bands in order to improve the vision further.

There are several studies comparing EST and EVL, which also include patients with active bleeding. The haemostatic efficacy of EVL varied from 80% to 100% and that of EST from 75% to 100%. Lo et al exclusively addressed the issue of the choice of method in active bleeding. They randomized 71 patients with active variceal bleeding to receive either EST or EVL. Initial haemostasis was achieved in 97% of the EVL group compared with 76% undergoing EST. The rate of re-bleeding (33% versus 17%) and the 4-week mortality (35% versus 19%) were higher in the EST group. Although the difference in mortality was not statistically significant, morbidity was significantly lower with EVL compared with EST (5% versus 29%). This study highlights the higher risk of complications associated with emergency EST and dispels the notion that EVL may be cumbersome in the presence of active bleeding.

Although active bleeding can be effectively controlled by either method, when these techniques fail and in cases of massive haemorrhage, variceal obliteration using cyanoacrylate (Histoacryl) can be life saving.

**Cyanoacrylate**

In many centres, massive life-threatening oesophagogastric variceal bleeding is managed by using the tissue glue. There are very few studies comparing the efficacy of Histoacryl with EST or EVL. In the experience of the Toronto group, Histoacryl was shown to be superior to EVL with regard to haemostasis.

Feretis et al compared glue injection plus sclerotherapy using polidocanol against polidocanol alone in a prospective randomized study of 126 patients and demonstrated the advantage of the combination in active bleeding. The re-bleeding rate in active bleeders was significantly lower with the combination therapy (10% versus 44%), as was the in-hospital mortality rate (14.2% versus 50%). Thakeb et al combined ethanolamine oleate (EO) and histoacryl and compared the combination against EO alone in a prospective randomized trial. They also observed a reduction in the re-bleeding rate (8.6% versus 25%).

However, studies from Hong Kong by Sung et al have not shown cyanoacrylate to be an attractive modality compared with either band ligation or sclerotherapy. It is worth mentioning that in both these studies the glue was used like a sclerosing agent. Cyanoacrylate is, however, a fast-solidifying substance appropriately used for the occlusion of actively bleeding varices. It is highly effective for prompt haemostasis in an emergency, as well as for obliterating large oesophageal or fundal varices. It does not
induce much inflammation and subsequent fibrosis of the oesophageal wall to prevent recurrence. Therefore, we routinely occlude the actively bleeding oesophageal varices with Histoacryl\textsuperscript{1} and use ligation and, if required, subsequent low-dose sclerotherapy for all other remaining varices.

The high complication rate observed in the cyanoacrylate group by Sung et al\textsuperscript{32} was mainly the result of ulceration, which was not mentioned in the second study.\textsuperscript{33} In fact, mucosal ulcerations always occur after injection, extruding the solidified glue. These superficial ulcers should therefore be considered as a normal consequence rather than a complication. Bleeding from such ulcers occurs only if the varix has not been completely obliterated during the initial injection. This is especially important in treating large gastric varices, for which it is necessary to inject all feeding vessels during the same session.

Although the polymerization of cyanoacrylate in contact with blood is supposed to be instantaneous, embolization of the solidified glue into the lung or even the brain has been reported in the literature.\textsuperscript{34–36} Use of the contrast agent lipiodol as a diluent has been implicated in such embolic episodes, and some endoscopists prefer to use the undiluted glue.\textsuperscript{37} This accelerates solidification and requires rapid injection. Another potential drawback is that, in the absence of lipiodol, it is not possible to assess the success of the glue injection radiologically.

Overall, the incidence of these complications is very low, and one must not overlook the fact that in the life-threatening situations in which it is to be used, there are very few alternatives.

**Fibrin glue**

In an effort to reduce the rate of complications associated with sclerotherapy, Zimmer et al investigated the utility of fibrin glue.\textsuperscript{38} In a randomized controlled trial, they compared polidocanol and fibrin glue in 36 actively bleeding oesophageal varices. At 4 weeks, re-bleeding was less common with the fibrin group, and there was no mortality, whereas five patients in the polidocanol group died. The incidence of treatment-induced ulcers was significantly lower with fibrin, and major complications occurred only with polidocanol. However, a wider experience is warranted to evaluate the cost-effectiveness and the potential risks of embolization associated with fibrin glue.

**Elective therapy: prevention of re-bleeding**

**Sclerotherapy**

Conventional sclerotherapy, introduced in 1939\textsuperscript{39}, has stood the test of time and remained the mainstay of treatment of oesophageal varices. It serves as the standard against which all evolving methods are compared. The principle behind EST involves the superficial injection of an inflammatory agent, which causes local tissue necrosis. The resulting process of scarring replaces the normal mucosa and submucosa with fibrotic connective tissue. This process eliminates varices, perforating veins but not the peri-oesophageal collaterals. Correctly applied in multiple sessions over a longer period of time, sclerotherapy induces fibrosis of the inner oesophageal wall, which is so far the only non-surgical means of preventing variceal recurrence and thus re-bleeding.

Despite decades of research on all conceivable aspects of the procedure, there is little consensus regarding methodology. The main variables include the sclerosant used
(ethanolamine oleate, polidocanol or sodium tetradecyl sulphate, hypertonic glucose, absolute alcohol or a combination of these agents), the technique of injection (intravariceal or paravariceal), the treatment schedule, concomitant therapy, etc. The most important drawback of sclerotherapy is the fact that it may be associated with serious complications. The frequency and severity of these complications vary in different studies, which underscores the fact that the technique is operator dependent.

Local ulcerations invariably occur in all patients and are not necessarily considered a complication since superficial trauma to the oesophageal mucosa and submucosa is a prerequisite for scarring. However, deep ulceration may lead to re-bleeding in 2–13%. Extensive ulcers cause pain and, when deeper, may even lead to perforation. The application of excessive amounts of sclerosant, and/or injection beyond the submucosa by using larger needles, increases this risk. The most important long-term complication of sclerotherapy is the development of oesophageal strictures in 7–59% of cases following the healing of deep ulcerations.

Minor complications such as fever, retrosternal pain and transient dysphagia occur in 50–60% of patients. Inflammation induced by the sclerosant may also result in pleural effusions, bacteraemia, pneumonia and even septicaemia. Significant complications occur in about 20%, which include deep oesophageal ulcerations, necrosis and perforation. Procedure-related mortality varies between zero and 5%.

**Endoscopic variceal ligation**

The introduction of EVL by Stiegmann and Goff in 1986 provided a safer and equally effective alternative. The principle of EVL is similar to that of haemorrhoidal ligation. Strangulation of the varix leads to thrombosis. The bands are displaced over 3–7 days with the ischaemic mucosal necrosis and sloughing of the thrombosed varix. Following variceal ligation, oesophageal ulcers invariably occur. They are usually superficial and heal faster than sclerotherapy-induced ulcers.

One major difference between ligation and sclerotherapy, as demonstrated in three comparative trials and a meta-analysis by Laine and Cook of seven randomized trials, is the reduced incidence of stricture formation (0–11% versus 19–33%). Bacteraemia and other infectious sequelae are significantly less frequent following EVL. An entirely preventable complication is food bolus impaction, and it is generally advisable to keep the patients receiving EVL therapy on a soft diet for at least 72 hours after the procedure. Serious complications such as bleeding or perforation following EVL are rare, most being related to the placement of an overtube while using single band ligators.

Multiband ligators with a possibility of placing 4–10 bands have eliminated the need for repeated introduction of the endoscope and thus the need for an overtube. Preliminary studies comparing single band ligators with multiligators indicate that the latter are safer and are associated with less patient discomfort and morbidity, and a reduced banding time.

**EST or EVL?**

Several studies have compared ligation with sclerotherapy and reported it as a safer and quicker technique with fewer episodes of re-bleeding and a lower complication rate. The earlier quoted meta-analysis by Laine and Cook also confirmed the reduction of the re-bleeding rate (odds ratio 0.52; 95% CI 0.37–0.74), overall mortality rate (odds ratio 0.67; 95% CI 0.46–0.98) and mortality caused by re-bleeding (odds ratio
0.49; 95% CI 0.24–0.996) with variceal ligation compared with EST.\textsuperscript{51} The number of sessions required to achieve variceal obliteration was lower. There was no significant difference regarding pulmonary infection or bacterial peritonitis, but the frequency of oesophageal strictures was less with ligation (odds ratio 0.10; 95% CI 0.03–0.29).

Following this meta-analysis, eight more randomized trials were published, demonstrating the superiority of EVL over sclerotherapy (Table 1).\textsuperscript{18,19,22,24,50,57–59} In the study of Lo et al\textsuperscript{22}, ligation was associated with a lower complication rate (5% versus 29%). Avgerinos et al observed an even higher complication rate of 60% in the sclerotherapy group, as against 35% in the ligation group.\textsuperscript{57} Sarin et al\textsuperscript{24} also observed a faster eradication rate requiring fewer sessions with ligation compared with the sclerotherapy group (4.1 ± 1.2 versus 5.2 ± 1.8). Although the actuarial recurrence of varices was higher after EVL (28.7% versus 7.5%), fewer patients re-bled (three versus 10) than with EST. Baroncini et al\textsuperscript{50} also observed a higher initial complication rate (31% versus 11%) with sclerotherapy, while the variceal recurrence was higher with ligation (30% versus 13%). Masci et al\textsuperscript{58} achieved a comparable eradication rate with EVL and EST (88% versus 82%), but ligation required fewer sessions (3.4 versus 5.3) and the complication rate was lower (18% versus 38%), similar to that seen in other studies. Re-bleeding before variceal eradication was significantly more frequent in the EST group; there was, however, no difference after eradication. Major complications of chronic oesophageal ulcers and strictures were significantly more with sclerotherapy (36% versus 10%).

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*Emergency endoscopic treatment; **stricture; EST = endoscopic sclerotherapy; EVL = endoscopic variceal ligation; bold print: $P < 0.05$.}
Hou et al reported on the long-term outcome of ligation versus sclerotherapy in 185 cirrhotics with a mean follow up of 55.3 ± 12.5 months. Although the variceal eradication rate was similar in both groups (88% versus 86%), the mean number of sessions for eradication was significantly lower in the ligation group (3.7 ± 1.7 versus 5.1 ± 2.2). While the overall frequency of recurrence was not reported, there were 99 re-bleeding episodes, 89 of which were related to portal hypertension. The re-bleeding rate was lower with EVL (24%; 20 patients with 30 episodes) than with EST (38%; 32 patients with 59 episodes). The risk of re-bleeding before achieving variceal eradication was also significantly higher in association with EST compared with EVL (13.11 ± 3.61 versus 6.47 ± 2.54 episodes per 100 patient-months), but it did not differ after eradication.

Among the sources of re-bleeding after eradication, bleeding from gastric varices was significantly higher among those treated by EST than by EVL (37% versus 8%). Other independent factors determining the risk of re-bleeding as seen on multifactorial analysis, were the Child–Pugh class and the presence of haematemesis or hæmatochezia. The overall survival was similar in both groups, the hepatic functional reserve being the only factor determining long-term survival on multivariate analysis.

Although attractive because of a faster eradication rate and fewer complications, ligation was shown to be associated with a higher variceal recurrence (30–48% versus 8–30%; see Table 1 above). The difference in variceal recurrence can be explained by the fact that the ulcers caused by banding are usually superficial and induce very limited scarring. Since the high portal pressure is not affected by endoscopic treatment and the perforating veins are not obliterated by ligation, unlike EST, the residual oesophageal varices dilate over a period of weeks or months. In an effort to use the best of both methods, thus minimizing the drawbacks, a combination of ligation and sclerotherapy is being explored.

Combination therapy: scleroligation or ligation and sclerotherapy?

Although only two techniques are being combined, the methods and results differ because of the variables involved (Table 2). Some authors have combined ligation and sclerotherapy during the same session (synchronous treatment) while others initially controlled the varices by ligation, followed by sclerotherapy of the small residual varices (metachronous treatment). Even those using a synchronous approach differed in their methodology in that some injected either above or below a ligated varix, others injected the ligated varix and still more ligated the injected varix. The results were compared against band ligation alone, sclerotherapy alone or both.

Synchronous approach. Takeuchi et al performed paravariceal sclerotherapy after ligation in 40 patients. Sixteen patients (40%) developed circumferential ulcers, leading to stricture formation in 11; however, they had no variceal recurrence over a 3-year follow-up. In the rest, who did not develop circumferential ulcers, the cumulative recurrence rate was 55–92%.

Six randomized trials compared combined therapy administered in the same session against monotherapy (Table 2). While achieving a marginally higher variceal eradication rate (71% versus 60%), Laine et al observed a higher complication rate (29% versus 10%) and required a higher number of sessions (4.9 ± 0.6 versus 2.7 ± 0.4) with the combination therapy compared with ligation alone. The re-bleeding rate and mortality were similar in both.
Saeed et al found the combination therapy to require a higher number of sessions for eradication (4.1 ± 0.6 versus 3.3 ± 0.4) and to be associated with higher mortality (eight patients versus four) and complication rates (65% versus 20%), including stricture formation (30% versus 10%), compared with ligation. Variceal recurrence and re-bleeding were also more frequent in the combination group (23% versus 16% and 36% versus 25%, respectively).

In two recent studies on the same subject, the results were contradictory. Umehara et al achieved similar eradication rates (81% versus 84%) with ligation as with combined therapy, the former requiring fewer sessions (2.3 ± 0.5 versus 3.5 ± 1.1). However, they noticed more complications in association with the combined therapy (68% versus 46%) while the variceal recurrence was very high with ligation alone (72% versus 22%). Al Traif et al reported higher mortality (23% versus 10%) and complication rates (34% versus 29%) with a surprisingly low variceal recurrence (6% versus 21%) following ligation compared with combination treatment.

On the other hand, Iso et al compared sclerotherapy (weekly injections of 5% ethanolamine) and combination treatment (initial ligation followed by sclerotherapy after 1 week). They found no significant difference in the eradication rate (80% versus 74%), hospitalization time (4.9 ± 1.9 versus 4.4 ± 1 weeks) and number of sessions (4.1 ± 0.8 versus 3 ± 0.5) between the groups. However, circumferential scarring and fibrosis could be achieved in 92% of the sclerotherapy group compared with only 22%.

<table>
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<td>3 ± 0.5</td>
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<td>Nishikawa (1999)</td>
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<td>-</td>
<td>3.9 ± 0.8</td>
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<td>14</td>
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<td>-</td>
<td>2.3 ± 0.5</td>
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<td>8</td>
<td>80.8</td>
<td>2.3 ± 0.5</td>
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<th>Author (year)</th>
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<th>Re-bleeding %</th>
<th>Eradication %</th>
<th>Sessions</th>
<th>Recurrence %</th>
<th>Deaths %</th>
<th>Complications %</th>
</tr>
</thead>
<tbody>
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<td>Bhargava (1997)</td>
<td>EVL+EST</td>
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<tr>
<td>Lo (1998)</td>
<td>EVL</td>
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<td>-</td>
<td>3.7 ± 0.9</td>
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<tr>
<td></td>
<td>EVL+EST</td>
<td>37</td>
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<td>3.4 ± 1.1</td>
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<tr>
<td>Masumoto (1998)</td>
<td>EST</td>
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<td>0</td>
<td>95</td>
<td>4.7 ± 1.4</td>
<td>10</td>
<td>0</td>
<td>50</td>
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<tr>
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<td>0</td>
<td>65</td>
<td>2.3 ± 0.8</td>
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<td>0</td>
<td>5</td>
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<tr>
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<td>EVL+EST</td>
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<td>0</td>
<td>86</td>
<td>4.1 ± 0.9</td>
<td>12</td>
<td>0</td>
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</table>

EST = endoscopic sclerotherapy; EVL = endoscopic variceal ligation; **bold print:** P < 0.05.
of the combination group. Accordingly, the rates of variceal recurrence were much lower after sclerotherapy alone (8% versus 39%).

Metachronous approach. Three randomized studies compared ligation or sclerotherapy alone with the combination of low-dose sclerotherapy following an initial reduction of the varices by EVL.\textsuperscript{65–67} Bhargava and Pokharna, in a study on initial outcome, reported higher eradication (87% versus 24%) and lower re-bleeding (19% versus 22%) with combination therapy, although the number of sessions required (5.9 ± 2.3 versus 4.3 ± 1.8) and the overall complication rate (44% versus 31%) were higher.\textsuperscript{65}

Lo et al reported on the additive effect of EST in patients receiving repeated ligation. The eradication rate and the number of sessions needed were similar in both groups.\textsuperscript{66} However, the mortality (2.7% versus 8.6%), re-bleeding (8% versus 31%) and variceal recurrence (14% versus 43%) rates were lower with combination therapy than with ligation alone.

Garg et al studied the outcome of sclerotherapy alone against the combination of ligation followed by low-dose EST.\textsuperscript{67} The variceal eradication rate and the number of endoscopic sessions required were similar in both. They noticed more complications (20% versus 3%) and re-bleeding (16% versus 3%) with sclerotherapy while the variceal recurrence and the cumulative probability of survival did not differ.

Ideally all three modalities – EST, EVL and EVL followed by low-dose EST – should be evaluated comparatively in order to observe their relative efficacy and safety. Although there is no such study for secondary prophylaxis, Masumoto et al reported their observations regarding the prevention of a first episode of bleeding in high-risk varices.\textsuperscript{68} The complication rate was lower in the combination group than with EST and was similar to that of EVL. The recurrence of varices was less than in the ligation group and comparable to the EST group, suggesting the additive effect of low-dose sclerosis on multiple ligation.

A critical analysis of the above studies reveals that the efficacy of every modality, especially that of sclerotherapy, is operator dependent which is likely to affect the final outcome of any comparison. There seems to be enough evidence that band ligation initially eradicates varices more quickly, but there is a higher variceal recurrence in the long term. Sclerotherapy is more suitable for complete eradication of residual varices than band ligation, especially when partial fibrosis of the oesophageal wall has occurred. Paravariceal injection of a small amount of sclerosant into the submucosa is easier to apply and unlikely to cause complications. The objective of treatment is to maintain variceal eradication rather than merely to obtain a reduction in variceal size. A judicious combination of band ligation for initial variceal eradication followed by sclerotherapy for any residual or recurrent varices, i.e. metachronous combination therapy, appears to reduce the frequency of local complications as well as variceal recurrence and re-bleeding.

Prophylactic endoscopic therapy

In the evolution of research on endoscopic treatment for portal hypertension, as sclerotherapy has established itself as the treatment of choice, some investigators have attempted to extend the method to the prevention of the index bleed. However, because of the inherent limitations of sclerotherapy, the outcomes have not been very encouraging. A meta-analysis of randomized trials of non-surgical treatment for the prevention of the first bleed in cirrhotics revealed that the incidence of variceal bleeding was significantly reduced with the use of propranolol (pooled odds ratio 0.54; 95% CI 0.39–0.74), especially in patients with large or medium-sized varices or in those
with a hepatic venous pressure gradient of over 12 mmHg, but there was only a trend towards a reduction in mortality. On the whole, the studies on prophylactic sclerotherapy were highly heterogeneous in the direction of bleeding and mortality rates so the effectiveness of this therapy remains undetermined.69

Miyoshi et al recently reported the long-term outcome of a randomized control trial on prophylactic sclerotherapy in 58 patients suffering from hepatoma with high-risk varices.70 Over 3 years of follow-up, there was a significant reduction in the bleeding rate (18% versus 50%) and an improvement in survival (37% versus 16%) following sclerotherapy. Although there seemed to be an improvement in survival in the treatment group, arterial embolization and percutaneous ethanol injection were also performed significantly more often in this group.

With the introduction of variceal ligation in the late 1980s, and the gradual replacement of EST by EVL as a safer alternative, the enthusiasm to find an endoscopic primary prophylaxis was revived (Table 3). Sarin et al, in a randomized controlled trial, observed a significant reduction in the number of patients who bled.71 However, the varices recurred in 29% of the patients, and there was no survival benefit over a follow-up of 14 months. Lay et al72 reported a significant reduction in the rate of variceal bleeding (19% versus 60%) and the 2-year cumulative mortality rate (28% versus 58%), while the recurrence rate was also high (42%). In this study, all recurrences were treated by sclerotherapy, which could have confounded the results. In another recent randomized controlled trial on prophylactic variceal ligation of high-risk varices, Lo et al observed that EVL reduced the frequency of bleeding in a subgroup of high-risk (Child–Pugh class B) patients and that there was a trend towards reducing the mortality from variceal bleeding.73

Only one study compared all the three modalities, namely sclerotherapy alone, ligation alone and combination therapy, for primary prophylaxis and followed the patients over 2 years after eradication of the varices.58 The complication rate was significantly lower with ligation and combined therapy than with EST (5% versus 10% versus 50%), while the recurrence of varices was lower with EST and combined therapy than ligation (10% versus 12% versus 40%). This study conclusively demonstrates that combination therapy helps to avoid the increased number of complications seen with

### Table 3. Randomized comparative trials of sclerotherapy, band ligation or a combination of both for the primary prophylaxis of variceal bleeding.

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>N</th>
<th>Method</th>
<th>Eradication %</th>
<th>Sessions N</th>
<th>Complications %</th>
<th>Mortality %</th>
<th>Follow-up (m)</th>
<th>Variceal bleed %</th>
<th>Recurrence %</th>
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<tbody>
<tr>
<td>Sarin (1996)</td>
<td>33</td>
<td>Control</td>
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<td>-</td>
<td>-</td>
<td>24.2</td>
<td>14 ± 5</td>
<td>39</td>
<td>-</td>
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<td>Lay (1997)</td>
<td>64</td>
<td>Control</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>58</td>
<td>24*</td>
<td>60</td>
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<td>Masumoto (1998)</td>
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<td>EST</td>
<td>95</td>
<td>4.7 ± 1.4</td>
<td>50</td>
<td>0</td>
<td>24</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>Lo (1999)</td>
<td>63</td>
<td>Control</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>37</td>
<td>29</td>
<td>22</td>
<td>-</td>
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<td>Sarin (1999)</td>
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<td>36#</td>
<td>11</td>
<td>14 ± 9</td>
<td>27</td>
<td>9</td>
<td>22</td>
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<td>Estevez (1999)</td>
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<td>EVL</td>
<td>89</td>
<td>3.2 ± 2.1</td>
<td>31</td>
<td>25</td>
<td>29</td>
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</tbody>
</table>

EST = endoscopic sclerotherapy; EVL = endoscopic variceal ligation; **bold print:** P < 0.05; † recurrences treated by sclerotherapy; * cumulative follow-up; # side-effects of propranolol; ## two patients died from ligation-induced ulcer bleeding.
sclerotherapy as well as the higher recurrence after ligation. Balancing the merits and
demerits of both methods, ligation followed by low-dose sclerotherapy seems to be an
optimum modality for the primary prophylaxis of high-risk oesophageal varices as well
as for secondary prophylaxis following a first variceal bleed.

Sarin et al recently compared prophylactic EVL with the widely accepted propranolol
therapy.74 The actuarial probability of bleeding was 15% and 43% respectively ($P = 0.04$).
Bleeding occurred in four patients in the EVL group, three of whom bled before variceal
eradication. The overall mortality related to variceal bleeding was identical. In two out
of the three deaths in the EVL group, fatal re-bleeding was ascribed to post-ligation
ulcers. In an accompanying editorial, Burroughs and Patch cautioned against the author’s
advocacy of primary prophylaxis with EVL. They were of the opinion that the high-risk
groups should be given non-selective beta-blockers and that ligation should be reserved
for patients showing contra-indications to or an intolerance of these drugs.75

Newer techniques: loops, snares and clips

Detachable mini-loops were invented as an alternative to single-band ligators to over-
come the disadvantages, such as the need for an overtube and for repeated reintro-
duction of the endoscope.76,77 This technique allows the placement of multiple loops
without requiring an overtube, and the transparent cylinder offers a nearly uninhibited
view. As with band ligation, the treatment causes superficial ulceration at the ligation
site.

Hachisu et al compared the use of single-band ligation with that of detachable
snares.76 The variceal eradication rate was comparable. The only reported complication,
pharyngeal injury, occurred with band ligation and was caused by the overtube.
However, whether the method has any significant advantage over the multiligator
systems, subsequently introduced, remains to be seen.

Shim et al, in a prospective randomized controlled trial, compared multiple band
ligation with mini-detachable snare ligation in 103 patients.78 They found the snare to be
comparable in terms of haemostasis, number of treatment sessions needed, re-bleeding
rate and recurrence rate, no serious complications occurring in either group.

Obvious advantages are the feasibility of placing multiple snares and the possibility
of using other endoscopic accessories following snare ligation without needing to
withdraw and re-introduce the scope. Disadvantages include the need for a double-
channel endoscope to facilitate flushing and irrigation during the procedure and also to
allow adequate suction. The long string tail of the closed loop may interfere with
subsequent ligation, which can be overcome by pushing the application catheter
further towards the gastric lumen after applying the snare. A recent modification has
been the introduction of ridged end-caps and an alteration in the angulation of the
endoloops to speed up delivery and improve efficacy. Hepworth et al used these
modified loops and found them to be more effective than injection or band ligation in
experimental haemostasis, as well as safe and effective in patients.79

Few investigators have used clips for treatment of varices. Ohnuma et al performed
the clipping of oesophageal and gastric varices in 12 children.80 The initial eradication
of oesophageal as well as gastric varices was achieved in all patients. Over a mean
period of 34.6 (range 9–48) months, and over 1–10 sessions, permanent eradication
was achieved in only three patients. Re-bleeding was related to treatment in one and
occurred from recurrent varices in two others. This method may fail to achieve
permanent variceal eradication and is unlikely to be cost-effective. It may, however, be
a useful option in mildly active bleeding.
ENDOSCOPIC HAEMOSTASIS OF GASTRIC VARICES

Gastric varices are the bleeding source in approximately 10–30% of patients suffering from variceal haemorrhage.\textsuperscript{81} Junctional varices are, like oesophageal varices, amenable to sclerotherapy or ligation.\textsuperscript{82,83} However, the most challenging gastric varices are the large conglomerates situated in the fundus. Kim et al studied, in 132 patients, the cumulative risk of haemorrhage associated with fundal varices that never bled.\textsuperscript{84} They reported a 16%, 36% and 44% cumulative risk of haemorrhage from these vessels at 1, 3 and 5 years, respectively. The size of the varices, the presence of red spots on the varices and the liver function (Child–Pugh class) were identified as significant independent risk factors for bleeding. Bleeding from large fundal varices is often torrential and requires surgery or liver transplantation.\textsuperscript{85} Various endoscopic options have been tried in the form of sclerotherapy, ligation, scleroligation, retrograde obliteration, glue injection, etc.

Sclerotherapy for gastric varices

Ever since endoscopic sclerotherapy became routine for oesophageal varices, it has also been attempted in the stomach, sometimes with disastrous results.\textsuperscript{81} Although there have been several reports, no prospective studies on sclerotherapy for gastric varices are so far available. Sarin retrospectively published his long-term experience of sclerosing gastric varices using absolute alcohol in 71 patients.\textsuperscript{86} Variceal obliteration could be achieved in 70–94.4% of gastro-oesophageal junctional varices compared with 41% of isolated fundal varices, with a re-bleeding rate of 53% in the latter group. One-quarter of the patients died over a mean follow-up period of 2 years. The author concluded that sclerotherapy is not suitable for isolated fundal varices and junctional varices along the greater curvature of the stomach. As these varices are probably collaterals of short gastric veins and retroperitoneal veins, endoscopy reveals only the ‘tip of the iceberg’.\textsuperscript{87}

Chang et al compared the injection of hypertonic (50%) glucose versus sodium tetradecyl sulphate in patients with cirrhosis who were Child–Pugh class C.\textsuperscript{88} The rate of initial haemostasis with hypertonic glucose and sodium tetradecyl sulphate were 92% and 80% respectively. However, early re-bleeding occurred in 30% and 70%, respectively, and repeating the sclerotherapy using the same agent achieved haemostasis in 70% and 21% of cases, respectively.

Przemioslo et al recently used bovine thrombin for the intravariceal injection of gastric varices in 52 patients.\textsuperscript{89} Initial haemostasis was achieved in 94% using a mean of 1070 IU thrombin in two sessions. The 72-hour mortality was 6%. At 6 weeks, the re-bleeding rate was 18% and the mortality 8%. The results are encouraging, and this substance requires further evaluation regarding the risk of embolization.

Ligation therapy

Cipolletta et al\textsuperscript{90} used detachable loops in seven cases of bleeding gastric varices and achieved haemostasis in all. Variceal size was significantly reduced in four, while the remaining three had persistently large gastric varices requiring cyanoacrylate injection. There was no re-bleeding over 2–6 months.

Yoshida et al reported a new technique combining sclerotherapy and ligation for gastric varices.\textsuperscript{91} The gastric varices were ligated using a detachable snare and residual varices in the surrounding area were initially sclerosed by ethanolamine oleate,
immediately followed by ligation of the injected varix using a pneumoactive device. Of the 35 patients receiving treatment (eight acute, six elective and 21 prophylactic), the gastric varices regressed in all and disappeared in 97%, without any serious complications. The 2-year cumulative variceal recurrence-free rate and survival rate were 85% and 80% respectively.

However, sclerotherapy as well as band ligation is unlikely to achieve the complete obliteration of extensive variceal conglomerates. Necroses caused by sclerotherapy or band ligation may lead to fatal haemorrhage. This limitation inherent to both methods can be overcome by cyanoacrylate injection.

**Histoacryl[^]**

Of all the different options, injection of cyanoacrylate is the only method that is being used effectively almost world wide, with the exception of the USA. In the presence of active bleeding from oesophageal and gastric varices, Histoacryl[^] allows for immediate and permanent haemostasis without the attendant morbidity and mortality of surgery.[^13] Cyanoacrylate was shown to be effective in the obliteration of gastric varices more than a decade ago.[^29-94] In patients with advanced liver disease, in whom surgery is associated with an exceptionally high risk, glue injection reduces mortality.

So far, only a few studies exist that contain detailed information on the use of Histoacryl[^] in the treatment of bleeding gastric varices. Using cyanoacrylate injection, Mostafa et al[^95] achieved an initial haemostasis rate of 100% in 100 patients with bleeding gastric varices. Re-bleeding occurred in 10 patients and was managed by repeated glue injection in six, while four required surgery. Five patients died of liver failure attributed to the bleeding episode and one of pulmonary embolism.

In a prospective, non-randomized study, Oho et al compared a single session of ethanolamine oleate injection with bucrylate for gastric variceal bleeding.[^96] The rate of primary haemostasis (no bleeding for 48 hours) was higher with bucrylate (93% versus 67%). The haemostasis rate was significantly higher with glue injection in fundal varices compared with cardiac varices. Although the re-bleeding (30% versus 25%) and complications (46% versus 41%) rates were similar with both substances, mortality was significantly reduced in the bucrylate group (67% versus 38%).

Ogawa et al recently proved the safety, superiority and durability of haemostasis by using cyanoacrylate in the emergency treatment of gastric variceal bleeding.[^97] They evaluated cyanoacrylate versus ethanolamine oleate in 38 patients undergoing emergency sclerotherapy and achieved complete haemostasis (lasting for 14 days or more) in 100% of the patients treated with glue as against 52.4% in the ethanolamine oleate group. There were no complications in either group. While 42.8% of the ethanolamine group required surgery after sclerotherapy, none were operated on in the Histoacryl[^] group. Although the cumulative survival rate did not differ between the groups, this also depending on the hepatic reserve, death from bleeding was prevented by using tissue glue.

Since Histoacryl[^] is not accepted for intravascular use, it has so far only been used in life-threatening variceal haemorrhage or when other methods have failed. Cyanoacrylate has recently been approved in Europe for endoscopic and intravascular use (Glubran, 2 GEM S.r.l., Italy). In the future, many prospective studies are expected using this drug.
REFERENCES


