Complications of endoscopic variceal therapy

J. M. SHAW, M.B. B.CH., F.C.S. (S.A.)
C. APOSTOLOU, M.B. CH.B., F.C.S. (S.A.)

Department of Surgery, University of Cape Town, MRC Liver Research Centre and Surgical Gastroenterology Unit, Groote Schuur Hospital, Cape Town

Bleeding from oesophageal varices is the most serious complication of portal hypertension and is the leading cause of cirrhosis-related deaths. One-quarter of cirrhotic patients who present with a first major variceal bleed die as a consequence of the bleed. After control of the index bleed, there is a 70% chance of rebleeding with a similar mortality. Survival after variceal bleeding depends largely on the rapidity and efficacy of control of the initial bleed, the presence and severity of underlying liver disease, and hepatic functional reserve.

Endoscopic injection sclerotherapy became an established method of controlling variceal bleeding worldwide following the initial prospective studies which were started in Cape Town in 1975, and the subsequent first randomised trial initiated in our unit. Endoscopic injection of tissue adhesive was pioneered by Gotlib and Zimmerman in 1984 and Soehendra in Germany in 1986. Endoscopic variceal ligation was introduced by Stieglmann in 1986 in Denver, Colorado.

Endoscopic treatment remains the principal first-line intervention in patients with bleeding oesophageal varices, both during the acute event and for long-term prevention of recurrent bleeding. Endoscopic haemostasis of actively bleeding varices has a greater inherent potential for major complications compared with other endoscopic procedures. Several technical variables may affect the outcome of any individual sclerotherapy session or combination of both. Most endoscopists perform sclerotherapy without accessories ('freehand technique'). Sclerotherapy is performed with different levels of skill and protocols using variable frequencies of injections and endoscopic surveillance. Several technical variables may affect the outcome of any individual sclerotherapy session or clinical trial. These variables include the type and concentration of the sclerosant solution, the injection site, injection volume and frequency of injections. Despite the widespread popularity of the procedure for control of acute variceal bleeding, sclerotherapy technique remains, to a great extent, empiric and individualised. Several basic issues of methodology remain largely unanswered. It is therefore not surprising that controlled trials comparing sclerotherapy with other specific therapies, including variceal ligation, have yielded conflicting results.

A variety of sclerosants are used with different mechanisms of action and varying complication rates. Tetradecyl sodium (1 - 3% solution), sodium morrhuate (5% solution) and ethanolamine oleate (5% solution) are the most commonly used sclerosant agents in the USA. Outside North America, 5% ethanolamine oleate and 1% polidocanol are used; polidocanol is usually used for paravarian injections. The ideal sclerosant and the best route of administration have yet to be defined, although the few controlled trials available favour ethanolamine oleate for intravarical and combined therapy.

Endoscopic tissue adhesive injection

Since their discovery in 1949, cyanoacrylates have been used as a tissue adhesive, embolisation material, and haemostatic agents in a broad range of medical specialties including orthopaedics, plastic and facial surgery, vascular surgery and interventional radiology. Tissue reactivity and toxicity of the short-chain cyanoacrylate monomers led to the synthesis of less histotoxic long-chain monomers, of which Histoacryl is the least histotoxic of the cyanoacrylate polymers available commercially. Two types of tissue adhesives, Histoacryl and Bucrylate, have been used to treat variceal bleeding (Fig. 1). These have proved effective in the control of bleeding with a 90% success rate. The fundamental technique of tissue
adhesive injection using N-butyl-2-cyanoacrylate (Histoacryl) is the same as sclerotherapy. Gotlib and Zimmerman first described the use of Bucrylate for endoscopic obliteration of oesophageal varices, and Soehendra et al. reported its use for gastric varices. The cyanoacrylate polymers have a viscosity and appearance similar to water. Polymerisation occurs on contact with water to form a solid complex tightly bound to underlying tissue. Polymerisation is almost immediate in blood. Experimental and clinical studies have shown that cyanoacrylate polymers have both bacteriostatic and haemostatic activity. Patients and personnel working with Histoacryl require eye protection or goggles as a precaution against inadvertent spraying of tissue adhesive during injection. Since the liquid tissue adhesive solidifies rapidly, any delay in withdrawing the injection needle from the varix after injecting the adhesive may result in the needle being trapped in the solidified cyanoacrylate mass. Leakage of adhesive may block the working channel of the endoscope and irreparably damage the instrument. This can be avoided by lubricating the insertion tube liberally with silicone oil and aspirating oil through the working channel. To prevent premature solidification during injection, Histoacryl is diluted with the oily contrast agent Lipiodol.

Endoscopic variceal ligation

Endoscopic variceal ligation (EVL) was developed as an alternative endoscopic method of treating oesophageal varices with the anticipation that EVL would be as effective as EIS, but with fewer complications. EVL uses small elastic ‘O’ bands which are stretched and loaded onto a cylinder attached to the tip of an end-viewing endoscope (Fig. 2). The varix is sucked into the cylinder, ensnared when the band is dislodged, and strangulated, leading to necrosis and sloughing of the thrombosed varix and band about a week later (Fig. 3). Six to eight elastic bands can be applied to the variceal columns during each endoscopy session.

Compared with sclerotherapy, EVL is less invasive because no sclerosant or sclerotherapy needle is used. However, there are technical drawbacks with EVL. The original single-band ligating device required repeated removal of the endoscope for reloading and reinsertion each time a new band was applied. An oesophageal overtube facilitated reintroduction but increased patient discomfort. Reloading the single-band ligator also prolonged the procedure, which was problematic especially during active bleeding or with poor patient tolerance. The single-band ligator has been replaced in most centres by the multiple-band ligator which carries six to ten bands (Fig. 4) and avoids the use of an overtube. A practical limitation of EVL is the suction cap on the tip of the endoscope, which reduces the field of vision by 30% and is a disadvantage when treating actively bleeding varices as blood and clot may pool in the suction cap and further reduce visibility. The new transparent caps have improved visibility. The standard disposable multiband ligators release individual bands by shortening the towlines around a rotating spindle mounted in the accessory port. In contrast, the recently available Euroligator is re-usable and releases each band by turning a wheel on the driver which applies tension to incrementally withdraw a flexible metal shaft.

Incidence of complications after endoscopic therapy

There is no consensus regarding the definition or classification of the complications that occur after the endoscopic treatment of oesophageal and gastric varices, and consequently the incidence varies widely in reported studies. Much of the published data are flawed because the reporting process is often biased with subjective and retrospective information, and complication rates are generally operator dependent. Comparative analyses of complication rates are hampered by variations in patient population, type and severity of liver disease and endoscopic technique used.
addition, differences in study design introduce a covert selection bias which may influence results. These biases include sampling and selection bias (specialist centres, expert endoscopists, different patient populations) confounding bias (emergency versus elective procedures) and measurement bias \(^5\) (incomplete reporting, delayed complications).

Many patients undergoing endoscopic variceal intervention have a limited prognosis, and therefore complications may not be identified or treated aggressively. The debilitated state of many patients undergoing endoscopic therapy contributes to the medical difficulties they encounter, often making differentiation of a true complication of the procedure difficult.\(^6\) Complication rates are also higher when carefully documented in prospective studies, while some studies express complication rates in terms of incidence per patient treated or per procedure performed.\(^7\) In long-term studies, repeated intervention also increases the cumulative risk of endoscopic-related complications in the individual patient.\(^7\) The most reliable data indicate that 10 - 15% of patients undergoing endoscopic variceal intervention will develop a major complication, but fewer than 1% of patients die as a direct result of the procedure.\(^7\)

**Classification of endoscopic complications**

Endoscopic-related complications have been categorised as (i) local effects involving the oesophagus, including ulceration, stricture and perforation; (ii) regional respiratory and cardiovascular effects; and (iii) distant or systemic consequences.\(^8\) Minor events have been defined as those that are self-limiting and do not require specific treatment, and do not interfere with the regular injection programme. Major complications are serious or life-threatening events that prolong hospitalisation.\(^8\)

**Endoscopic injection sclerotherapy**

Important factors influencing the complication rate are the experience of the endoscopist, the specific injection technique employed, the use of ancillary devices including overtubes or balloon tamponade, and whether sclerotherapy is performed as an emergency or elective procedure.\(^9\) Other interrelated anatomical factors are the close proximity of the oesophagus to vital mediastinal structures, repetitive breaching of the mucosa, and the potential for pulmonary and systemic spread of sclerosant through portal venous collaterals.\(^5,7,15,23,27\)

**Oesophageal complications**

**Morphological changes**

Oesophageal complications of EIS are invariably the consequence of excessive sclerosant-induced submucosal or transmural necrosis.\(^7\) The few studies that have examined the local histopathological effects of sclerosant on the oesophageal wall in detail have been based on autopsy studies. Although the injection techniques, type and volume of sclerosant used, and intervals between injections vary in these studies, the histopathological findings are remarkably similar and provide a time-dependent morphological profile of the effects of EIS on the oesophagus.\(^5,15-41\)

The earliest changes in the oesophageal wall, which occur during the initial 48 hours after injection of sclerosant, are thrombosis in superficial veins, submucosal oedema, and minor areas of tissue necrosis.\(^5\) Mucosal ulceration is uncommon during this early phase.\(^42\) After 48 hours, progressive tissue necrosis occurs, predominantly in the superficial layers and to a lesser extent in the deeper tissues (Fig. 5). During the first week, mucosal ulceration and a marked acute polymorphonuclear leucocyte inflammatory response occur, which is followed by an intense macrophage and fibroblast infiltration.\(^34,43\) Some residual varices remain patent while others contain thrombi in the early stages of endothelial and fibroblastic organisation.\(^40,44\) The extent of sclerotherapy-induced ulceration varies from small linear superficial defects to extensive ulcers.\(^5\) While most ulcers are limited to the submucosa or inner layer of the muscularis propria, a few extend more deeply into the muscularis propria. A quarter of autopsy specimens show transmural necrosis, which may progress to mediastinitis.\(^46\)

![Fig. 5. Mucosal slough at the site of a recent sclerotherapy injection.](Image)

The later chronic reaction is characterised by an evolution from granulation tissue to mature collagen with an accompanying chronic inflammatory cell infiltrate that becomes less prominent with time.\(^7\) Necrosis and ulceration may persist for up to 3 weeks. Organised thrombi and fibrosis become evident 1 month after injection.\(^39,60\) Fibrosis is usually limited to the submucosa and the inner muscularis propria but may occur as a localised transmural breach in muscle or as diffuse transmural fibrosis encasing residual varices.\(^43\) Marked thickening of the oesophageal wall is present in some specimens.\(^42\)

**Ulceration**

Small areas of superficial mucosal ulceration are a common finding in the lower oesophagus after EIS.\(^5,46\) Some reports consider ulceration to be an inevitable and necessary consequence of effective sclerotherapy.\(^7,46\) The prevalence and extent of ulceration is related to the type of sclerosant injected, method of injection,\(^55\) interval between injections\(^54,56\) and size of varices.\(^57\) Ulceration is reported to occur more frequently in Child’s C patients and after injection of large varices.\(^57\) There is evidence that increasing volumes of sclerosant may be implicated in deep ulceration, and the incidence increased with the associated use of balloon tamponade.\(^54,59\)

In a randomised study comparing the two injection techniques, no significant difference was found in the incidence of ulceration between paravariceal and intravariceal injections using 50% ethanol.\(^51\) The risk of ulceration may be related more to the intensity of the sclerotherapy programme.
than to the specific injection technique. In most instances, minor areas of superficial ulceration are asymptomatic and heal rapidly without the need for specific treatment.

To prevent sclerotherapy-induced ulcers and their complications, sucralfate, H2-receptor blockers and antacids, alone or in combination, have been used. While sucralfate may reduce rebleeding from ulceration, the frequency and extent of ulcers are similar in patients who had not received sucralfate. A controlled trial suggested that ulcer healing may be accelerated by sucralfate, especially in patients with deep ulceration. Ulcers healed more slowly in patients with a serum albumin level less than 3 g/dl.

A small proportion of sclerotherapy-induced ulcers persist, despite prolonged treatment with high-dose H2-receptor antagonists and sucralfate (Fig. 6). In a small group of patients with complicated chronic ulcers, complete healing was achieved in all after an 8-week course of 40 mg omeprazole daily. The rapid healing of resistant ulcers with omeprazole suggests that such ulcers may be perpetuated by mucosal damage from continuing gastroesophageal reflux. It is suggested that consideration be given to earlier use of omeprazole for post-sclerotherapy ulcers complicated by symptoms or bleeding.

**Fig. 6. Mucosal ulceration involving one quadrant of the oesophagus.**

**Bleeding**

Minor bleeding may occur from the needle puncture site after intravariceal injection of large varices, but it usually stops spontaneously. Bleeding that persists can be controlled by an adjacent small-volume submucosal injection or by direct tamponade using the side of the flexed tip of the endoscope. More severe bleeding results from inadvertent variceal laceration or accidental entry of the needle sheath into the varix in a restless or heaving patient. This can be prevented by withdrawing the needle into the sheath between injections.

Early recurrent major bleeding is the most common life-threatening event after sclerotherapy and occurs in 20 - 35% of patients. Urgent endoscopy is important to establish whether recurrent bleeding is from a varix, sclerosant-induced ulceration, oesophagitis, or another source. If recurrent bleeding is variceal in origin, further sclerotherapy is indicated. Although control of acute variceal bleeding is usually achieved with a single injection session in 70% of patients, some require further injections. If variceal bleeding recurs despite two apparently adequate injections, mortality increases exponentially and some other definitive procedure should be used.

Bleeding from ulceration after EIS may be particularly troublesome and occurs in up to 13% of patients. It may be difficult to exclude a variceal component aggravating the bleeding because of the complex venous anatomy of the lower oesophagus. Further injection of sclerosant is inappropriate if deep ulceration or oesophagitis is present, and may compound the problem. In most ulcers, bleeding is self-limiting or stops with the addition of octreotide and sucralfate. The small number of patients who continue to bleed pose a major management problem. Balloon tamponade increases the risk of pressure necrosis and perforation. Oesophageal transection may be hazardous after several previous injection sclerotherapy sessions and shunt surgery is inappropriate in cirrhotic patients with poor liver function.

In this difficult situation, the Liverpool group were able to control severe bleeding in 20 of 22 patients using intravenous somatostatin.

**Perforation**

In a small cohort of patients deep ulceration with transmural necrosis may progress to a localised or contained perforation without mediastinitis or communication with the pleural cavity. Confined perforations should be suspected in patients who have persistent pain and pyrexia after EIS. The diagnosis is confirmed on gastrogafin swallow. Treatment is conservative with intravenous antibiotics, parenteral hyperalimentation or enteral feeding via a fine-bore silastic nasoduodenal tube. Subsequent sclerotherapy should be delayed for 2 months until complete healing has occurred.

Free perforation occurs in 2 - 3% of patients and has a prohibitive mortality, especially in patients with advanced liver disease. Perforation occurred more frequently with the rigid oesophagoscope and was due to instrumental injury. Perforation after flexible injection sclerotherapy is usually delayed and is the result of deep ulceration and transmural necrosis. The risk of perforation is highest in patients who require repeated injections for uncontrolled or recurrent bleeding during the index admission. During these sessions, cumulative volumes of sclerosant are often used, and the risk of inadvertent misplaced, deep injections is greatest. Possible aggravating factors predisposing to delayed perforation include concurrent balloon tamponade, impairment of healing secondary to poor liver function, mucosal ischaemia associated with infusion of vasopressin, prolonged nasogastric intubation and colonisation of the ulcer base with Candida.

Oesophageal perforation generally presents 10 - 14 days after the index injection session. Analysis of patients in whom detailed clinical information is available reveals a prodrome with several features in common. The majority developed deep local ulceration at the injection site following urgent or emergency sclerotherapy during their index admission. Most patients had severe, prolonged retrosternal and pleuritic chest pain, fever, an exudative pleural effusion and worsening encephalopathy. The effusions were initially sterile, but invariably became infected with a variety of organisms. Gram-negative septicaemia, shock and deteriorating liver function with multi-organ failure was a common outcome despite surgical or tube drainage.
patients may not manifest the clinical features of an oesophageal leak but present with subtle signs of sepsis, worsening encephalopathy or deteriorating liver function, and the diagnosis is only made at autopsy.21,78,87

Free oesophageal perforation poses a major management problem.21 Oesophageal necrosis, mediastinal venous collaterals and sepsis with multiple organ failure preclude conventional treatment for oesophageal perforation.21 At thoracotomy the tissues are friable and oedematous, making repair difficult and likely to break down.62 In most reports, the majority of perforations were managed conservatively with tube thoracostomy and had a high mortality.60-67 This reflects the reluctance to institute major operative treatment in high-risk patients who have already been considered to have a poor prognosis.21,92

Intramural haematoma

Intramural haematoma of the oesophagus is a rare complication of EIS and has a reported incidence of 0.3 - 1.6%.88 The precise pathogenesis is speculative. Tissue necrosis extending into the submucosa and muscularis may be the initiating event and may be compounded by repeated injections.89 Raised portal pressure and coagulation defects89 may aggravate intramural dissection and extension of blood and sclerosant both longitudinally and circumferentially in the oesophageal wall.90,91 Tissue necrosis is at its most severe during the first 3 - 4 days after sclerotherapy and this may explain the early manifestation of this complication.92 Other factors implicated in the pathogenesis include the different injection techniques (paravariceal versus intravariceal injection), the type of sclerosant solution, the volume of sclerosant given per injection, the interval between treatments and the occurrence of retching or prolonged valsalva during or shortly after injection sclerotherapy.89,92

An intramural oesophageal haematoma should be suspected in a patient who presents with the triad of sudden-onset dysphagia, odynophagia and haematemesis or bloodstained sputum occurring soon after variceal sclerotherapy.93-95 There may however be no evidence of blood loss or haematemesis if the haematoma is contained within the oesophageal wall or submucosa and the mucosa has not been breached, in contrast to patients with a Mallory-Weiss tear, who present with upper gastrointestinal bleeding with or without pain and no dysphagia.96 Associated retrosternal chest pain is common and is due to epithelial separation by the expanding intramural haematoma. The absence of subcutaneous emphysema in the neck differentiates this condition from the more serious complication of oesophageal perforation.96 In a patient who has recently had EIS and has a clinical presentation compatible with an intramural haematoma of the oesophagus, contrast studies provide the simplest way of confirming the diagnosis and excluding an oesophageal perforation (Fig. 7).88 The contrast study may reveal a ‘double-barrel’ oesophagus in which contrast material can be seen in both the lumen of the oesophagus and the intramural cavity.97,98 An elongated radiolucent filling defect with a smooth outline is another radiological feature.94,96 Oesophagoscopy is helpful in establishing the diagnosis but should be reserved for inconclusive cases because of the invasive nature of the investigation.88 If performed, endoscopy usually shows a characteristic dark blue intramural bulge of mucosa97 (Fig. 8). Other imaging studies include computed tomography (CT) scan, magnetic resonance imaging (MRI) and oesophageal echo-endoscopy.

Fig. 7. Barium swallow showing an oesophageal intramural haematoma.

Fig. 8. Sclerotherapy-induced intramural oesophageal haematoma.

Treatment depends on a definitive diagnosis of intramural oesophageal haematoma.88 In contrast to patients with oesophageal perforation after EIS, which has a poor prognosis and who may require urgent surgical intervention, patients with intramural haematoma have a good prognosis.21 The initial treatment of intramural haematoma should be conservative.99 Symptoms usually begin to resolve spontaneously within 36 - 72 hours and disappear completely in 2 - 3 weeks.100 Patients should be kept nil per mouth and receive intravenous fluids. Oral feeds are introduced gradually as tolerated.99 Resolution of the intramural haematoma occurs by reabsorption without disruption of the mucosal surface in patients with small haematomas, or sloughing of the overlying mucosa may occur if the intramural haematoma is large.94,101 No adverse long-term sequelae have been reported after intramural haematoma formation and in most cases oesophageal varices had disappeared and were absent on follow-up oesophagoscopy.98
Stricture

The incidence of oesophageal strictures after EIS ranges from 10% to 15%. In 204 patients undergoing long-term sclerotherapy, 1 in 10 developed a stricture. While some reports have not found a direct relationship with the number of previous EIS sessions, volume or type of sclerosant and site of injection, Sorensen and the Cape Town group demonstrated a clear relationship between frequency and cumulative volume of injection and an association with pre-existing ulceration. Patients who developed a stricture had received more injections and larger volumes of sclerosant and a significantly greater number had preceding mucosal necrosis.

Sclerotherapy-induced strictures are usually short and localised to the lower 5 cm of the oesophagus (Fig. 9). Most strictures are easily dilatable and two to three dilatation sessions suffice in 85% of patients. Persistent oesophageal dysmotility may explain the refractory dysphagia which occurs in some patients despite adequate dilatation. Dilatation does not precipitate bleeding from partially treated varices and although the stricture may temporarily delay eradication of varices, the EIS programme can be continued successfully after stricture dilatation. For short symmetrical strictures, Maloney mercury-filled rubber dilators allow easy and safe dilatation while tighter and longer strictures require fluoroscopically controlled dilatation over an endoscopically placed guidewire with Savary dilators.

Motility disorders

Several studies have evaluated both the short- and long-term effects of sclerotherapy on oesophageal motor function and gastroesophageal reflux. Serial evaluation of motility patterns in the oesophagus before sclerotherapy, 3 days after sclerotherapy and 6 months later has demonstrated that the length of the high-pressure zone, peristaltic velocity and swallow-wave symmetry are markedly affected. The length of the high-pressure zone increased significantly after the initial sclerotherapy session owing to intense inflammation in the distal oesophagus. The normal waveform pattern and symmetry are altered substantially by sclerotherapy. Double- and triple-peak waveforms, dropped swallow waves in the distal oesophagus and simultaneous and spontaneous contractions have been documented. Oesophageal function after eradication of varices using oesophageal scintigraphy has shown increased transit times compared with controls. These changes increase after sequential treatment, and this effect is probably a manifestation of sclerosant-induced oesophagitis, intramural inflammatory response or fibrotic changes in the oesophageal wall.

Injection sclerotherapy does not substantially affect lower oesophageal sphincter pressure. There is some disagreement concerning the incidence and severity of gastroesophageal reflux after EIS and its effect on oesophageal acid clearance. Reilly et al. found that gastroesophageal reflux, as determined by standard reflux tests, becomes more prevalent after sclerotherapy and suggested that reflux contributed to stricture formation. In contrast, Ogle et al. found no instance of acid reflux into the oesophagus but patients who received sclerotherapy did have impaired acid clearance. The magnitude of these changes is not thought to be severe enough to promote pathological gastroesophageal reflux.

A variety of other unusual local oesophageal complications have been reported after sclerotherapy. Pneumatosis intestinalis and pneumoperitoneum may occur due to intramural air entering through a small mucosal tear in the oesophageal wall and dissecting distally into the stomach, small bowel and colon. Rupture into the peritoneum produces free intraperitoneal air. The condition is benign and resolves spontaneously. Other rare complications include pseudo-diverticula, mucosal bridges and periesophageal granulomas. These are usually incidental findings and require no specific therapy.

Cardiorespiratory effects

Cardiac complications specifically related to EIS are rare. Anecdotal reports of coronary artery spasm, persistent bradycardia, and heart failure due to polidocanol have been reported. Seven cases of pericarditis after sclerotherapy have been described. The onset is heralded by fever, chest pain and dyspnoea and a pericardial friction rub is present with electrocardiographic and echocardiographic evidence of a pericardial effusion. If pericarditis remains undiagnosed, progression to cardiac tamponade or constrictive pericarditis may occur.

Pulmonary complications are common and range from minor asymptomatic changes found incidentally on routine chest radiographs to aspiration or bronchopneumonia, pleural effusions, lobar collapse or consolidation and adult respiratory distress syndrome. It is often difficult to determine to what extent respiratory changes are directly attributable to EIS as aspiration, sepsis, pulmonary congestion due to fluid shifts after vigorous resuscitation with crystalloids, massive transfusion, and diaphragmatic splinting by tense ascites are additional factors that may contribute to a deterioration in pulmonary function.

Several studies have investigated the distribution and potential damaging effects of sclerosant solutions on the respiratory system. There is evidence that sclerosant dissemination to the pulmonary and systemic circulation after intravariceal EIS occurs through oesophagogastric collaterals and the azygous-hemiazygous systems. Entry of sclerosant...
into the pulmonary circulation has been demonstrated to occur by positive uptake on lung scan of technetium-99m (Tc99m)-tagged STS and SM solutions when injected into oesophageal varices.\(^\text{21}\) Systemic dissemination has also been demonstrated to occur with ethanolamine-Tc99m sodium pertechnetate, but the frequency and consequences appear to be minor.\(^\text{150-152}\)

Since premedication and passage of an endoscope may contribute to aspiration pneumonitis or hypoxaemia, the incidence of respiratory dysfunction in patients receiving EIS should be compared with that in patients undergoing endoscopy for other reasons. In a controlled study no difference was found in either the short- or long-term effects on lung function and gas exchange after EIS in patients with cirrhotic portal hypertension compared with a similar group undergoing diagnostic endoscopy only.\(^\text{133}\) In contrast, patients complaining of post-injection retrosternal pain 24 hours after EIS had a larger fall in vital capacity and forced expiratory volume than patients without pain.\(^\text{141}\) One-third of cirrhotic patients with oesophageal varices were shown to have pre-existing pulmonary interstitial oedema and arterial hypoxaemia (PAO\(_2<80\) mmHg). In these patients injection of 5% ethanolamine olate may lead to a further deterioration of pulmonary function and a decrease in arterial oxygen content.\(^\text{119}\)

Pulmonary and mediastinal abnormalities are frequently found on routine chest radiographs and CT when performed within 48 hours after EIS. These changes may be explained by peri-oesophageal inflammation and the lack of serosa covering the oesophagus. Saks \textit{et al.} found radiological changes in up to 79% of patients.\(^\text{135}\) Pleural effusions and mediastinal soft-tissue densities are the most common findings, while atelectasis, linear lung shadows and retrocardiac soft-tissue densities are demonstrated less often.\(^\text{119,135}\) Chest pain and effusions occur more frequently in patients who develop deep ulceration and is due to an intense peri-oesophageal, mediastinal and pleural inflammatory reaction.\(^\text{119,141}\) Most effusions are small and resolve spontaneously.

Aspiration is the most serious respiratory complication and occurs most frequently during EIS for acute bleeding.\(^\text{21}\) Aspiration pneumonia is avoidable if the stomach is emptied by suction before sclerotherapy and an assistant scrupulously clears the mouth and hypopharynx with a suction catheter during injection. Excessive sedation, hepatic encephalopathy, and a prolonged procedure without adequate or effective airway protection during active bleeding are contributing factors if bleeding is massive. In this situation endotracheal intubation before endoscopy is essential to avoid this potentially lethal complication.\(^\text{21}\) Other uncommon pulmonary complications reported after EVS are bronchooesophageal fistula,\(^\text{137}\) pneumothorax,\(^\text{139}\) subcutaneous emphysema\(^\text{140}\) and chylothorax.\(^\text{139}\)

**Systemic complications**

**Septicaemia and bacteraemia**

Transient fever after sclerotherapy occurs in a quarter of patients due to an acute local inflammatory response or chemical phlebitis. If a fever persists for more than 2 days, a search for a septic or local oesophageal complication is mandatory. Anecdotal reports have incrimented EIS as a cause of meningococcal and \textit{Streptococcus pneumoniae} septicaemia,\(^\text{140}\) infective endocarditis,\(^\text{141}\) pyogenic meningitis,\(^\text{142}\) brain\(^\text{145-146}\) and perinephric abscesses\(^\text{147}\) and bacterial peritonitis.\(^\text{148,149}\) These reports have raised the question whether the incidence of septic complications is increased as a consequence of EIS-induced bacteraemia.

There are several possible sources of bacterial contamination during injection sclerotherapy.\(^\text{21}\) The spectrum of organisms associated with bacteraemia and the predominance of alpha-haemolytic streptococcus strongly suggest oropharyngeal flora as the source of contamination. During sclerotherapy these organisms may be introduced by the endoscope or injector needle and enter the bloodstream. The length of the needle injector and a contaminated water supply have been implicated in EIS-associated bacteraemia.\(^\text{150,151}\) The incidence of bacteraemia after EIS ranges from 0% to 50%.\(^\text{150}\) A variety of injection techniques and sclerosant solutions and different lengths of injection needles were used in these studies. An increased incidence of bacteraemia occurs during and up to 5 minutes after EVS. Because blood cultures were drawn during both these periods in fewer than half of the studies, the extent of bacteraemia in some studies may have been underestimated.\(^\text{119}\) Inherent in all studies using positive blood cultures is the difficulty of determining true bacteraemia from contaminants.\(^\text{21}\) Some investigators have isolated common skin commensals and in one study, 23% of isolates were coagulase-negative staphylococcus\(^\text{155}\) which may originate from the skin during venepuncture.

Most previous data on bacteraemia after sclerotherapy have been obtained from blood cultures during elective EIS.\(^\text{21}\) The risk of bacteraemia may be higher during technically more demanding and traumatic emergency sclerotherapy and in the presence of venous and urine catheters and endotracheal tubes. In addition, alcoholic cirrhotics may develop bacteraemia spontaneously owing to decreased reticuloendothelial system function, impaired neutrophil chemotaxis, low levels of serum complement and impaired cell-mediated immunity.\(^\text{150}\) The clinical importance of blood culture isolates after sclerotherapy remains questionable. In none of the prospective studies have organisms (other than probable commensals) been isolated more than 30 minutes after sclerotherapy, suggesting that bacteraemia is always transient. Furthermore, no infective complications have been reported following bacteraemia in these studies. Previous recommendations advising routine antibiotic prophylaxis are no longer valid and most authorities now recommend prophylaxis only for patients with specific vascular risk factors, such as prosthetic valves or previous endocarditis.\(^\text{150}\) Strict attention to routine equipment cleaning and disinfection to avoid contamination of endoscopes and the water supply are essential.\(^\text{21}\)

**Haemodynamic and thrombotic effects**

Potential effects of repeated long-term EIS and obliteration of oesophageal varices are an increase in portal pressure, the development of other compensatory collaterals and bleeding from varices at remote sites.\(^\text{160-162}\) Despite an improvement in laboratory and clinical parameters of hepatic function, the portal venous pressure gradient increased by a third in cirrhotic patients after eradication of oesophageal varices.\(^\text{163}\) Six of 15 patients (40%) with non-alcoholic portal hypertension developed spontaneous spleno-adreno-renal shunts following sclerotherapy.\(^\text{141}\) The same mechanism may explain the increased incidence of portal hypertensive
gastropathy after repeated EVS\textsuperscript{106} and the phenomenon of bleeding from varices at other sites, including duodenum, ileum, colon, rectum and bowel-related adhesions.\textsuperscript{106,112,113,117}

Changes and direction of flow in the coronary and azygos systems are complex in portal hypertension. Phasic retrograde oesophageal collateral flow has been demonstrated during EIS using fluoroscopy and endoscopic Doppler flow techniques.\textsuperscript{169} Intra-operative portography has demonstrated that flow may be hepatofugal, to and fro or hepatopetal.\textsuperscript{170} There is concern that altered venous flow, endothelial damage and a hypercoagulable state after repeated intravariceal EIS may promote excessive local venous thrombosis with propagation into the splanchnic venous system and thrombosis of the portal and splenic veins. Some authors claim that a local endothelial inflammatory response after EIS is the initiating event, while others have shown that hypercoagulable states may be induced by sclerosant.\textsuperscript{111-113} In an umbilical cord model designed to simulate variceal blood flow, brief exposure to even low concentrations of STS produces damage and stripping of endothelium which exposes highly thrombogenic factor VIII-rich subendothelium.\textsuperscript{115} The effects of STS on coagulation and platelet function are dependent on sclerosant concentration. Dilute STS induces a hypercoagulable state by selective inhibition of protein C, and promotion of platelet aggregation. Activation of systemic blood coagulation in cirrhosis after sclerotherapy, which may be aggravated by vasopressin infusion, may promote venous thrombosis in the splanchnic bed. In experimental studies higher concentrations of STS inactivate the coagulation cascade and cause lysis of platelets.\textsuperscript{171}

Since EIS may lead to thrombosis of gastric varices,\textsuperscript{42} it is conceivable that thrombus may extend and initiate thrombosis in the splanchnic venous system. Portal vein thrombosis is a well-recognised complication of cirrhosis and portal hypertension. The reported incidence ranges from 0.5\% to 21\%.\textsuperscript{114-116} Acute portal or mesenteric venous thrombosis in association with EIS is, however, uncommon. Seven cases of portal or mesenteric venous infarction have been reported following EIS or intravenous vasopressin.\textsuperscript{117,118} Stoltenberg \textit{et al.}, in an autopsy series, demonstrated extension of thrombus from oesophageal varices into the portal and mesenteric venous systems resulting in small-intestinal infarction and hepatic failure.\textsuperscript{181} In 2 cases splenic vein thrombosis and splenic infarction occurred suggesting propagation of clot via both coronary and left gastric veins.

Distant histological effects due to sclerosant, including intimal damage and fibrosis in the portal vein, have been reported after obliteration of oesophageal varices. Hunter \textit{et al.} found substantial changes when comparing the morphology of portal and splenic veins in patients who had received EIS with those who had not.\textsuperscript{132} In addition to the loss of smooth muscle and elastin fibres and medial fibrosis present in patients with portal hypertension, those who had received EIS also had disruption of normal venous architecture with loss of elastic fibres, smooth-muscle bundles and an increase in fibrous tissue. Changes in splenic vein histology have been demonstrated in patients undergoing splenorenal shunt after EIS which included increased fibrosis, intimal and medial destruction and microthrombi.\textsuperscript{145} Retrograde flow, flow through collateral pathways or abnormal responses of the perivenous lymphatic vessels to the sclerosant may, alone or in combination, account for the changes seen.\textsuperscript{142} An increased incidence of thrombosis of the portal vein or its major tributaries after long-term sclerotherapy has been disputed. In the Emory controlled trial comparing EIS with distal splenorenal shunt, all patients underwent angiographic assessment of the portal, splenic and superior mesenteric veins before and after treatment.\textsuperscript{184} Those who received chronic EIS provided a unique group in whom the incidence of thrombosis could be assessed. Despite frequent injections (mean 6.5) and large volumes (mean 62 ml), no patient developed splenic or portal vein thrombosis.\textsuperscript{184}

### Tissue adhesive injection

Endoscopic oblitative therapy with Histoacryl is now the first-choice treatment for emergency control of acute gastric variceal bleeding\textsuperscript{13,185,186} Histoacryl polymerises immediately on contact with blood, resulting in rapid haemostasis.\textsuperscript{28} The major complications related to tissue adhesive injection are damage to endoscopic equipment due to premature hardening of cyanoacrylate, local mucosal ulceration at the injection site and embolisation of liquid adhesive before polymerisation has occurred.\textsuperscript{28} Cementation and fixation of the injection needle in the glued varix is a serious complication.\textsuperscript{187} Endoscopic extraction of an adherent injector is difficult. Laser disintegration\textsuperscript{188} of the solidified Histoacryl mass or amputation of the catheter above the impacted needle are two suggested retrieval options before operative removal is considered.

Common minor complications of the procedure include fever and chest pain due to the inflammatory response.\textsuperscript{189} Major complications include ulceration and recurrent bleeding.\textsuperscript{28,29} Acute and chronic inflammatory changes secondary to Histoacryl injection include perivascular inflammation and vessel-wall necrosis with a foreign body reaction. Perigastric abscesses may follow perivascular inflammation with infection.\textsuperscript{189} Endoscopic obliteration of varices with bucrylate was found to cause acute ulcerations of the oesophageal wall in autopsy studies. However, no ulceration has been documented when Histoacryl injections are strictly intravariceal, in contrast to inadvertent paravariceal injection, which can cause extensive ulceration. Approximately 1 week after intravariceal injection of Histoacryl, the mucosa overlying the obliterated varix begins to slough. The solid tissue adhesive is treated as a foreign body and is gradually extruded into the lumen. Several months may elapse before the Histoacryl is completely eliminated from the stomach wall. This usual sequence of events following Histoacryl injection is not associated with increased bleeding or other adverse events.\textsuperscript{28,29}

Serious complications such as embolisation to the portal vein, lung and spleen have been reported.\textsuperscript{190,191} Rare complications include splenic infarction and splenic abscess, bacterial pericarditis, leakage through the gastro-renal shunt into the left renal vein and inferior vena cava, systemic embolisation including pulmonary, cerebral and coronary embolisation, portal and splenic vein thrombosis.\textsuperscript{192-195} Other complications include bacteremia and visceral fistulas. Risk factors for extravascular embolisation with Histoacryl treatment include a large injection volume, the dilution of radiolucent Histoacryl with radiopaque Lipiodol and the existence of shunts.\textsuperscript{181} In 140 patients who had Histoacryl
injection for bleeding gastric varices, radiographically evident pulmonary emboli were observed in 6 (4.3%). In comparison with patients without emboli, these patients received a higher mean volume of injection (4.2 v. 1.8 ml) \( (p = 0.0011) \). Four of the 6 patients with pulmonary emboli had respiratory symptoms. Chest radiographs and CT scans showed unusual tubular or nodular, radiopaque pulmonary emboli along the pulmonary vessels. Multiple peripheral, wedge-shaped, subsegmental perfusion defects were seen on perfusion lung scans. In 5 of 6 patients the radiographic abnormalities showed complete or partial resolution. There were no fatalities directly associated with pulmonary emboli.

A prospective randomised study compared the efficacy and complications of cyanoacrylate injection and band ligation in cirrhotic patients with gastric variceal bleeding.\(^{196}\) Group A, who received cyanoacrylate injection, comprised 31 patients and group B, who had band ligation, 29 patients. Active bleeding was present in 15 patients in group A and 11 patients in group B. Treatment was repeated regularly until obliteration of gastric varices. Initial haemostasis (defined as no bleeding for 72 hours after treatment) was 87\% in group A and 45\% in group B \( (p = 0.03) \). The sessions required to achieve variceal obliteration and obliteration rates were similar in both groups. However, rebleeding rates were significantly higher in group B (54\%) than group A (31\%) \( (p = 0.0005) \). Treatment-induced ulcer bleeding occurred in 2 patients (7\%) in group A and 8 patients (28\%) in group B \( (p = 0.03) \). The amount of blood transfusion required was higher in group B than group A \( (4.2 \pm 1.3 \text{ v. } 2.6 \pm 0.9 \text{ units}) \) \( (p < 0.01) \). Nine patients in group A and 14 patients in group B died \( (p = 0.05) \). The data suggested that endoscopic control and subsequent eradication using cyanoacrylate was more effective and safer than band ligation in patients with bleeding gastric varices.\(^{197}\)

**Endoscopic variceal ligation**

The initial technical complications of variceal ligation related to the use of the overtube that facilitated extraction and re-insertion of the endoscope with the use of the original single-shot ligator which required removal to load each new ‘O’ ring. Complications associated with the use of the overtube include oesophageal mucosal tears, variceal rupture with massive bleeding, oesophageal perforation and separation of the overtube from the bite block.\(^{13,14}\) Placement of the overtube caused injury to the oesophagus by pinching mucosa between the gastroscope and the edge of the overtube when the endoscope was used as an obturator to facilitate introduction of the overtube or with repeated reinsertion of the gastroscope.\(^{13,14,194}\) Specific precautions are now recommended when an overtube is used and important modifications in the design and technique have reduced the risk of overtube trauma. Design changes in the overtube include a smoothly tapered distal end to reduce the risk of pinching oesophageal mucosa, a precurved shape to fit the pharynx and a change in the shape of the mouthpiece to prevent rotation of the overtube. Many endoscopists use an oesophageal bougie dilator, which completely fills the lumen of the overtube as an obturator. The development of a multiple-band ligator has eliminated the need for an overtube.\(^{13}\) Separation of the plastic barrel of the multi-band ligation set has occurred if the silastic collar loosens, or the ligator cap may dislodge if there is a size mismatch between the ligator cap and the endoscope.\(^{196}\) Grasping forceps or a balloon catheter are useful tools to retrieve the dislodged component from the oesophagus or stomach.

Oesophageal ulcers caused by EVL are more superficial and resolve faster than sclerotherapy-induced ulcers.\(^{31,32}\) A prospective randomised clinical study by Young et al.\(^{200}\) compared ulcers induced by sclerotherapy with those caused by ligation. Sclerotherapy-induced ulcers were significantly deeper than those induced by ligation (1.8 mm v. 0.6 mm). However, the ligation-induced ulcers were significantly larger in surface area and more circular than the linear lesions induced by sclerotherapy. Ligation-induced ulcers healed at a mean of 14 days compared with 21 days for those resulting from sclerotherapy. These findings confirm earlier clinical and laboratory observations that the majority of ligated sites (whether in the stomach or oesophagus) slough and produce consistent shallow ulcerations from 3 to 7 days after application.

Oesophageal band ligation-induced bacteremia occurs far less often than with sclerotherapy and is associated with fewer significant infectious sequelae such as spontaneous bacterial peritonitis or pneumonia. Berner et al.\(^{201}\) studied the short-term risks of bacteremia, changes in pulmonary and coagulation functions, oesophageal motility, and gastroesophageal reflux in a prospective randomised trial of sclerotherapy versus variceal ligation. Although the numbers of patients were small, there were no significant differences with respect to pulmonary and coagulation parameters or bacteremia. However, oesophageal dysmotility and evidence of reflux were more common in patients undergoing sclerotherapy. Patient acceptance of ligation procedures was better than for sclerotherapy sessions.

**Comparative efficacy and complications of endoscopic variceal treatment**

**EVL compared with EIS**

Data from 13 peer-reviewed prospective randomised controlled trials comparing the efficacy and complications of EVL and EIS have been published in full and are summarised in Table I. The first study by Stiegmann et al. found band ligation to have improved survival and fewer complications.\(^{12}\) Laine et al. reported a significant reduction in local complications but no difference in rebleeding or mortality.\(^{202}\) Gimson et al. reported that band ligation obliterated the varices more rapidly and reduced the incidence of rebleeding but without affecting mortality or complications.\(^{203}\) Lo et al. documented that ligation reduced rebleeding, mortality and complications and achieved obliteration more rapidly.\(^{204}\) Hou et al. found that EVL was superior to EIS in reducing rebleeding and complications but not mortality.\(^{205}\) Eradication was achieved in fewer treatment sessions in the trials reported by Sarin et al.\(^{206}\) and Barocci et al.\(^{207}\) with clear benefit in terms of fewer procedure-related complications. Avgierinos et al. found that EVL eradicated varices more swiftly than EIS and with fewer complications.\(^{208}\) Masci et al. recorded significantly more major complications with EIS (36\% v. 10\%).\(^{209}\)

De la Pena et al. found similar rates of variceal eradication, but eradication was accomplished sooner and with fewer complications in patients undergoing EVL.\(^{210}\) In 84 patients
with schistosomal and post-hepatitic cirrhosis, Fakhry et al. required significantly fewer treatment sessions to eradicate varices and fewer complications with EVL. In 73 adult patients with bleeding oesophageal varices due to extrahepatic portal vein obstruction, Zargar et al. found that EVL achieved variceal eradication with significantly fewer endoscopic sessions and fewer complications than EIS. A meta-analysis of the seven initial randomised trials concluded that EVL reduced the rebleeding rate (odds ratio (OR) 0.52; 95% confidence interval (CI) 0.37 - 0.74), mortality rate (OR 0.67; CI 0.46 - 0.98), and rate of death due to bleeding (OR 0.49; CI 0.24 - 0.99) compared with EIS. Oesophageal strictures occurred less frequently with EVL (OR 0.10; CI 0.03 - 0.29). The number of endoscopic treatment sessions required to achieve variceal obliteration was lower with EVL than with EIS. On the basis of lower rates of rebleeding, mortality, and complications and the need for fewer endoscopic treatments, EVL should be considered the endoscopic treatment of choice for patients with bleeding oesophageal varices.

EVL compared with combination therapy (EVL plus EIS)

The combination of EVL and synchronous EIS should theoretically achieve more rapid variceal eradication, as the sclerosant is injected into a stagnant varix above the ligation site. Laine et al. compared EVL with combination therapy (EVL plus EIS) and found that EVL achieved significantly less rebleeding, mortality, and complications than EIS.

TABLE 1. RANDOMISED TRIALS COMPARING ENDOSCOPIC SCLEROTHERAPY WITH BAND LIGATION

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Patients</th>
<th>Group</th>
<th>Sessions</th>
<th>Rebleed (%)</th>
<th>Variceal bleeding (%)</th>
<th>Complications (%)</th>
<th>Recurrence (%)</th>
<th>Eradication (%)</th>
<th>Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stiegmann (1992)</td>
<td>65</td>
<td>EIS</td>
<td>5 ± 2</td>
<td>48</td>
<td>52</td>
<td>22</td>
<td>50</td>
<td>56</td>
<td>55</td>
</tr>
<tr>
<td></td>
<td>64</td>
<td>EVL</td>
<td>4 ± 2</td>
<td>36</td>
<td>48</td>
<td>2</td>
<td>33</td>
<td>55</td>
<td>72</td>
</tr>
<tr>
<td>Laine (1993)</td>
<td>39</td>
<td>EIS</td>
<td>6.2 ± 0.4</td>
<td>44</td>
<td>31</td>
<td>56</td>
<td>NA</td>
<td>69</td>
<td>85</td>
</tr>
<tr>
<td></td>
<td>38</td>
<td>EVL</td>
<td>4.1 ± 0.3</td>
<td>26</td>
<td>24</td>
<td>NA</td>
<td>59</td>
<td>89</td>
<td></td>
</tr>
<tr>
<td>Gimson (1993)</td>
<td>49</td>
<td>EIS</td>
<td>4.90</td>
<td>53</td>
<td>51</td>
<td>57</td>
<td>NA</td>
<td>71</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td>53</td>
<td>EVL</td>
<td>3.40</td>
<td>30</td>
<td>24</td>
<td>67</td>
<td>NA</td>
<td>82</td>
<td>52</td>
</tr>
<tr>
<td>Lo (1995)</td>
<td>59</td>
<td>EIS</td>
<td>6.5 ± 1.2</td>
<td>51</td>
<td>36</td>
<td>19</td>
<td>NA</td>
<td>63</td>
<td>68</td>
</tr>
<tr>
<td></td>
<td>61</td>
<td>EVL</td>
<td>3.8 ± 0.4</td>
<td>33</td>
<td>13</td>
<td>3</td>
<td>NA</td>
<td>74</td>
<td>84</td>
</tr>
<tr>
<td>Sarin (1997)</td>
<td>48</td>
<td>EIS</td>
<td>5.2 ± 1.6</td>
<td>21</td>
<td>13</td>
<td>3</td>
<td>NA</td>
<td>87</td>
<td>79</td>
</tr>
<tr>
<td></td>
<td>47</td>
<td>EVL</td>
<td>4.1 ± 1.2</td>
<td>38</td>
<td>38</td>
<td>NA</td>
<td>92</td>
<td>94</td>
<td></td>
</tr>
<tr>
<td>Baroncini (1997)</td>
<td>54</td>
<td>EIS</td>
<td>4.0 ± 0.1</td>
<td>19</td>
<td>30</td>
<td>31</td>
<td>13</td>
<td>93</td>
<td>78</td>
</tr>
<tr>
<td></td>
<td>57</td>
<td>EVL</td>
<td>3.5 ± 0.1</td>
<td>22</td>
<td>11</td>
<td>39</td>
<td>93</td>
<td>79</td>
<td></td>
</tr>
<tr>
<td>Avgerninos (1997)</td>
<td>40</td>
<td>EIS</td>
<td>5.8 ± 2.7</td>
<td>47</td>
<td>25</td>
<td>60</td>
<td>44</td>
<td>97</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>37</td>
<td>EVL</td>
<td>3.7 ± 1.9</td>
<td>27</td>
<td>14</td>
<td>35</td>
<td>31</td>
<td>93</td>
<td>78</td>
</tr>
<tr>
<td>Hou (1999)</td>
<td>84</td>
<td>EIS</td>
<td>5.1 ± 2.2</td>
<td>38</td>
<td>32</td>
<td>NA</td>
<td>NA</td>
<td>86</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>84</td>
<td>EVL</td>
<td>3.7 ± 1.7</td>
<td>24</td>
<td>32</td>
<td>NA</td>
<td>88</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Masci (1999)</td>
<td>50</td>
<td>EIS</td>
<td>5.3</td>
<td>42</td>
<td>38</td>
<td>27</td>
<td>82</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>EVL</td>
<td>3.4</td>
<td>12</td>
<td>14</td>
<td>18</td>
<td>32</td>
<td>88</td>
<td>NA</td>
</tr>
<tr>
<td>De la Pena (1999)</td>
<td>46</td>
<td>EIS</td>
<td>5.3 ± 1.6</td>
<td>50</td>
<td>30</td>
<td>41</td>
<td>28</td>
<td>71</td>
<td>78</td>
</tr>
<tr>
<td></td>
<td>42</td>
<td>EVL</td>
<td>6.6 ± 2.4</td>
<td>31</td>
<td>12</td>
<td>14</td>
<td>25</td>
<td>79</td>
<td>81</td>
</tr>
<tr>
<td>Fakhry (2000)</td>
<td>41</td>
<td>EIS</td>
<td>4.8 ± 0.9</td>
<td>15</td>
<td>10</td>
<td>65</td>
<td>20</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>43</td>
<td>EVL</td>
<td>2.8 ± 0.5</td>
<td>16</td>
<td>12</td>
<td>2</td>
<td>21</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>*Zargar (2005)</td>
<td>36</td>
<td>EIS</td>
<td>7.7 ± 3.3</td>
<td>19</td>
<td>19</td>
<td>22</td>
<td>9</td>
<td>92</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>37</td>
<td>EVL</td>
<td>3.7 ± 1.2</td>
<td>3</td>
<td>3</td>
<td>11</td>
<td>95</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

*Extrahepatic portal venous obstruction. NA = data not available. Significant differences between EVL and EIS are underlined.
TABLE II. RANDOMISED TRIALS COMPARING ENDOSCOPIC BAND LIGATION WITH LIGATION PLUS SIMULTANEOUS SCLEROTHERAPY

<table>
<thead>
<tr>
<th>Author (year) (patient numbers)</th>
<th>Patients</th>
<th>Group</th>
<th>Sessions</th>
<th>Re-bleed</th>
<th>Variceal bleeding</th>
<th>Complications (recurrence)</th>
<th>Eradication (survival)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laine (1996) (N = 41)</td>
<td>20</td>
<td>EVL</td>
<td>2.7 (0.4)</td>
<td>30%</td>
<td>25%</td>
<td>10%</td>
<td>60% (85%)</td>
</tr>
<tr>
<td>Saeed (1997) (N = 47)</td>
<td>25</td>
<td>EVL</td>
<td>4.9 (0.6)</td>
<td>29%</td>
<td>19%</td>
<td>29%</td>
<td>71% (86%)</td>
</tr>
<tr>
<td>Umehara (1999) (N = 51)</td>
<td>26</td>
<td>EVL</td>
<td>3.3 (0.4)</td>
<td>25%</td>
<td>86%</td>
<td>25%</td>
<td>(16%) (84%)</td>
</tr>
<tr>
<td>Al Traif (1999) (N = 60)</td>
<td>29</td>
<td>EVL</td>
<td>4.1 (0.6)</td>
<td>36%</td>
<td>63%</td>
<td>65%</td>
<td>(23%) (64%)</td>
</tr>
<tr>
<td>Saeed (1999) (N = 47)</td>
<td>25</td>
<td>EVL</td>
<td>2.3 ± 0.5</td>
<td>NA</td>
<td>NA</td>
<td>46%</td>
<td>81% (91%)</td>
</tr>
<tr>
<td>Masumoto (1999) (N = 51)</td>
<td>26</td>
<td>EVL</td>
<td>3.5 ± 1.0</td>
<td>NA</td>
<td>NA</td>
<td>68%</td>
<td>84% (100%)</td>
</tr>
<tr>
<td>Al Traif (1999) (N = 60)</td>
<td>29</td>
<td>EVL</td>
<td>3.6 ± 0.5</td>
<td>23%</td>
<td>10%</td>
<td>34%</td>
<td>81% (100%)</td>
</tr>
<tr>
<td>Djurdjevic (1999) (N = 80)</td>
<td>51</td>
<td>EVL</td>
<td>3.9 ± 0.3</td>
<td>14%</td>
<td>10%</td>
<td>36%</td>
<td>(29%) (88%)</td>
</tr>
<tr>
<td>Argonz (2000) (N = 94)</td>
<td>41</td>
<td>EVL</td>
<td>2.3 ± 0.7</td>
<td>17%</td>
<td>7%</td>
<td>29%</td>
<td>86% (90%)</td>
</tr>
<tr>
<td>Hou (2001) (N = 94)</td>
<td>47</td>
<td>EVL</td>
<td>3.7 ± 1.2</td>
<td>23%</td>
<td>NA</td>
<td>NA</td>
<td>(40%) (87%)</td>
</tr>
</tbody>
</table>

NA = data not available.
Significant differences between EVL and EIS are underlined.

TABLE III. RANDOMISED TRIALS COMPARING ENDOSCOPIC BAND LIGATION WITH LIGATION PLUS CONSECUTIVE SCLEROTHERAPY

<table>
<thead>
<tr>
<th>Author (year) (patient numbers)</th>
<th>Patients</th>
<th>Group</th>
<th>Sessions</th>
<th>Re-bleed</th>
<th>Variceal bleeding</th>
<th>Complications (recurrence)</th>
<th>Eradication (survival)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bhargava (1996) (N = 50)</td>
<td>21</td>
<td>EVL</td>
<td>4.3 ± 1.8</td>
<td>NA</td>
<td>19%</td>
<td>31%</td>
<td>24% (NA)</td>
</tr>
<tr>
<td>Lo (1998) (N = 72)</td>
<td>35</td>
<td>EVL</td>
<td>3.7 ± 0.9</td>
<td>31%</td>
<td>5.4%</td>
<td>NA</td>
<td>(43%) (NA)</td>
</tr>
<tr>
<td>Masumoto (1998) (N = 41)</td>
<td>20</td>
<td>EVL</td>
<td>2.3 ± 0.8</td>
<td>0%</td>
<td>0%</td>
<td>5%</td>
<td>65% (100%)</td>
</tr>
</tbody>
</table>

NA = data not available.
Significant differences between EVL and EIS are underlined.
sclerotherapy (EVL/EIS) in 41 patients. Twenty-one patients randomised to EVL/EIS had their oesophageal varices ligated then 1 ml of sclerosant (1.5% sodium tetradecyl sulfate) injected into the varix immediately above the ligature. However, the anticipated benefits were not realised in this study, which reported similar eradication, rebleeding and death rates in the two groups (Table II). More treatment sessions (rather than fewer) were required to achieve eradication in the combined treatment arm, which caused more complications than EVL alone. Similar results were reported by Saeed et al., Al Traif et al., Djurdjevic et al., Argonz et al. and Hou et al., who reported that control of acute bleeding, rebleeding rates, variceal eradication rates, and mortality were similar in the two treatment groups (Table II). However, more endoscopy sessions were required to achieve eradication with combination therapy, which was associated with a higher incidence of deep mucosal ulceration, dysphagia and oesophageal strictures.

A meta-analysis found no significant differences between EVL and EIS combined versus EVL alone in terms of oesophageal rebleeding (relative risk (RR) 1.05; 95% CI 0.67 - 1.64; p = 0.83), death (RR 0.99; 95% CI 0.68 - 1.44; p = 0.96) or number of endoscopic sessions to variceal obliteration (RR 0.23; 95% CI 0.055 - 0.51; p = 0.11). However, the incidence of oesophageal strictures was significantly higher in the EVL plus EIS group than in the EVL-alone group. The meta-analysis of these studies suggests that little is to be gained by the addition of low-dose sclerotherapy to standard ligation techniques. Based on the available evidence, synchronous treatment with EVL and EIS provides no additional benefit and is associated with higher patient morbidity.

(b) Sequential combination (EVL + EIS) therapy

Recognising the technical limitations of EVL and synchronous EIS, Bhargava and Pokharna adopted a more pragmatic approach to combination therapy (Table III). Patients were randomised to either EVL alone, or to the combination of EVL and sequential EIS. Combination therapy used repeated EVL until the varices were reduced in size to grade II, followed by weekly small-volume sclerotherapy to achieve complete eradication. Overall the combined treatment cohort required more endoscopic sessions (5.9 ± 2.3 v. 4.3 ± 1.8; p < 0.05), but re-bleeding rates (19% v. 22%) and complication rates were similar in the two groups. This study suggested that a staged approach to combination therapy was better, as it achieved 100% variceal eradication without the associated high rate of iatrogenic complications normally associated with EIS. In their study Lo et al. found that eradication and number of sessions needed were similar in both groups. However, the mortality (2.7% v. 8.6%), rebleeding (8% v. 31%) and variceal recurrence (14% v. 43%) rates were lower with combination therapy than with EVL alone. Masumoto et al. found no difference in their study.

EIS alone compared with combined EVL and EIS therapy

Iso et al. compared EIS alone with a step-wise combination of EVL as initial treatment followed by weekly EIS (Table IV). There were significantly fewer iatrogenic complications with the combined EVL/EIS strategy. Garg et al. found that more complications (20% v. 3%) and rebleeding (16% v. 3%) occurred with sclerotherapy alone. In the study by Shigemitsu et al. eradication was achieved with significantly less sclerosant in the combined EVL/EIS group (17 v. 25 ml, p < 0.05). Nishikawa et al. found that the number of treatment sessions for eradication was significantly lower (2.3 v. 3.9, p < 0.001) for EVL and EIS, and that in total less sclerosant was used.
Strategies to prevent endoscopic-related complications

Endoscopic therapy is an established and integral part of the management of acute variceal bleeding and the long-term treatment of patients after a variceal bleed. Although complications after endoscopic therapy for variceal bleeding are common, most are minor and do not interrupt the treatment programme. In a small group of patients, however, the success of therapy is compromised by recurrent bleeding and serious procedure-related complications. Most of the serious complications related to endoscopic therapy occur in patients with severe liver disease in whom control of bleeding is difficult. It is not the complication that is a breach of optimal care, but rather the failure to anticipate or recognise it and respond appropriately. Mature clinical judgement is necessary in acute problematic or complex cases, and careful supervision of trainees or assistance by an experienced endoscopist becomes essential when critical decisions are required. Early and close multidisciplinary consultation is often useful in demanding cases to facilitate appropriate therapy and optimal management.

A number of critical generic precautions are important to avoid both local and systemic complications, regardless of the type or technique of endoscopic intervention used to control acute bleeding. Effective resuscitation should precede endoscopy in patients with evidence of recent major bleeding. Diagnostic and therapeutic endoscopy should be performed in a well-equipped unit with competent assistance and careful monitoring. It is prudent to perform endoscopy with the minimum sedation needed for a safe procedure. High-risk patients and those with significant cardiopulmonary disease need only topical oropharyngeal anaesthetic spray and the minimum intravenous sedation. In a frail patient, a benzodiazepine alone may be safer than the combination of a benzodiazepine and an opiate. Medications used for sedation should be titrated to the desired level of sedation using small, incremental doses. Flumazenil, a benzodiazepine antagonist, and naloxone, an opiate antagonist, must be available should a cardiopulmonary complication occur. Meticulous attention should be given to suctioning of the mouth and hypopharynx by a dedicated assistant to avoid aspiration.

Early endotracheal intubation is crucial if major bleeding occurs. Precise and accurately placed injections are essential. To ensure adequate visibility during active bleeding, a large or double-channel endoscope with vigorous irrigation should be used with the head elevated. Uncontrolled blind, large-volume injections during active bleeding must be avoided. The sclerotherapy needle should not exceed 5 mm in length and a short bevel reduces the risk of deep injections. Recurrent bleeding after EIS requires careful evaluation and repeat endoscopy to determine the source. If variceal bleeding continues or recurs during the index admission despite two adequate injections, other definitive therapy should be instituted.

If ulceration involves more than one oesophageal quadrant, further injections should be delayed until healing has occurred. Treatment with H2-blockers or sucralfate does not prevent ulceration, but may accelerate healing. Omeprazole has been effective in the treatment of chronic ulcers. Special care should be taken in patients with deep ulceration and persistent pain, fever, an increasing pleural effusion and deterioration of liver function, which suggest transmural necrosis and impending perforation. Motility abnormalities are usually transient in nature and of minor clinical consequence and most symptomatic strictures respond effectively to dilatation.

In countries where cyanoacrylate adhesive is available and licensed for endoscopic use, damage to the endoscopic equipment, ulceration and pulmonary embolism are the main potential complications that restrict its use. Damage to the endoscope is preventable if specific precautions are taken. There have been documented cases of cerebral, pulmonary and portal embolism. These complications appear to be related to the volume of cyanoacrylate injected. The volume should be limited to 4 - 6 ampoules (2.0 - 3.0 g) per session. Cerebral and pulmonary embolism appears to depend on the presence of an abnormal right-left vascular communication.

Variceal eradication with EVL requires fewer endoscopic treatment sessions, and causes substantially fewer oesophageal complications. Although the incidence of early gastrointestinal rebleeding is reduced by EVL in most studies, this does not result in an overall survival benefit relative to EIS. Simultaneous combination therapy (EVL + EIS) of large varices confers no advantage over EVL alone. A staged approach with initial EVL followed by EIS when varices are small requires further evaluation as the sequential combination may prove to be the optimal method of minimising variceal recurrence. Overall, current data demonstrate clear advantages for using EVL in preference to EIS. EVL should therefore be regarded as the endoscopic technique of choice in the treatment of oesophageal varices.

The range of treatment options for bleeding oesophageal varices has expanded markedly during the past two decades. The treatment of acute bleeding and prevention of recurrent variceal bleeding is best accomplished by a skilled, knowledgeable, and well-equipped team using a multidisciplinary integrated approach. Optimal management should provide the full spectrum of treatment options, which include pharmacological therapy, endoscopic treatment, interventional radiological procedures, surgical shunts and liver transplantation.

This review is based in part on an invited lecture by Professor J. E. J. Krige at the Inaugural Tri-Nations Gastroenterology Meeting on ‘Current Topics in Gastroenterology’ at Bunker Bay, Margaret River, Western Australia, on 8 March 2005 and a chapter on ‘Complications of endoscopic sclerotherapy’ by J. E. J. Krige et al.

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