

Injection therapies for variceal bleeding disorders of the GI tract (CME)

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Over the past 20 years, an endoscopy has become an integral part of the treatment for variceal-related bleeding disorders of the GI tract. There are essentially 2 effective endoscopic therapies: mechanical therapy via banding ligation and injection therapy. Of the injection therapies, sclerosants and tissue adhesives are the most studied. The appeal of injection therapy is its simplicity, portability, and affordability. The basic mechanisms of action of these solutions include sclerosis, thrombosis (via endogenous clotting mechanisms or the formation of a plastic cast), and vascular tamponade. This review will summarize the indications, technique, and the most current data that support the use of endoscopic injection therapies on variceal-related-bleeding GI disorders.

REVIEW METHODOLOGY

Key words, including “endoscopic injection,” “gastrointestinal bleeding,” and “varices,” and with limits to human clinical studies in English, were used to search the PUBMED database through May 2006. A manual search of citations from relevant articles was also performed. The strength of reported evidence based on reviewed studies were ranked according to “Evidence based gastroenterology and hepatology” (Appendix 1).¹

ESOPHAGEAL VARICES

Variceal hemorrhage is responsible for up to 10% of upper-GI bleeding.² Among patients with cirrhosis, mortality attributed to bleeding from varices is as high as 50%.³ Rebleeding is common without intervention and is highest during the first 6 weeks, necessitating a reliable secondary prophylaxis strategy.⁴ Injection therapy has been studied in primary prophylaxis, acute hemostasis, and secondary prophylaxis.

Sclerosants

Sclerosants are the most commonly used injection agent in treating esophageal varices. As an injection therapy,

they are easily available, simple to use, and less costly than alternative therapies.^{5,6} Sclerotherapy was first described in 1939 by Crafoord and Freckner, and the first randomized trials to show efficacy in hemostasis and improvement in survival took place in the early 1980s.^{5,7,8} Although the current consensus of evidence favors endoscopic variceal ligation in treating esophageal varices, injection sclerotherapy remains an effective endoscopic treatment (Table 1).⁹

Sclerosants used to treat varices include sodium morrhuate, 5% ethanolamine oleate, 1% polidocanol, absolute ethanol, sodium tetradecyl sulfate, hypertonic glucose, and 3% phenol.^{6,10-13} No particular agent has demonstrated superiority, and, as a consequence, different agents are used throughout various parts of the world. Sodium tetradecyl sulfate and sodium morrhuate are popular in the United States, whereas ethanolamine oleate is popular in Europe. In countries with limited resources, absolute ethanol remains popular, because of its relative affordability, despite concerns of severe esophageal ulceration and stenosis related to its use.^{5,14,15}

Unlike endoscopic variceal ligation, there is no accepted standard technique for the injection of sclerosants. One common disparity of opinion lies between intravariceal and paravariceal injection. In the intravariceal technique, sclerosant is injected directly into the varix. In general, the first injection of 1 to 2 mL is placed 1 cm below the active bleeding site, if that site is identified. All visible varices are then injected with 1 to 2 mL of sclerosant at the gastroesophageal (GE) junction. More proximally, injections are placed in 3-cm to 5-cm intervals up to 10 cm from the GE junction, unless an even more proximal bleeding site is identified. The advantage of sclerotherapy is rapid thrombosis, which leads to subsequent hemostasis and fibrosis. Approximately 10 to 20 mL of sclerosant is used per session, based on the size and number of varices.⁵ Ethanol is an exception in that injection of no more than a 4-mL volume is recommended in an intravariceal fashion.¹⁴

In the paravariceal technique, 1 to 2 mL of sclerosant is injected in the submucosa adjacent to the visible varices. The first injection starts at the GE junction and can be repeated circumferentially and proximally up to 10 cm, up to 20 to 50 times during a single or several sessions. The subsequent inflammation and fibrosis around the vessel wall

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TABLE 1. Summary of various injection therapies in the treatment of variceal-related bleeding GI disorders and level of evidence

Injection therapy	Acute hemostasis, %	Rebleeding, %	Level of evidence, grade*
1) Esophageal varices			
a) Sclerosants ^{5,7,8,10-13,25-41,43-46,55,57-61}	70-100	9-39	A
b) N-butyl-2-cyanoacrylate ⁸⁰⁻⁸⁵	84-100	28	A
c) Fibrin glue ⁸⁸	Not reported	28	A
2) Gastric varices			
a) Sclerosants ^{96,98-100}	52-67	25-43	A
b) N-butyl-2-cyanoacrylate ^{94,99,100,102-108}	58-100	0-40	A
c) 2-octyl-cyanoacrylate ¹¹⁵	100	4	B
d) Thrombin ¹¹⁷⁻¹¹⁹	75	25	B
e) Fibrin glue ^{120,121}	70-93	0-26	B
3) Rectal varices			
a) Sclerosants ¹²⁵⁻¹²⁸	Case reports	Case reports	C
b) N-butyl-2-cyanoacrylate ^{129,130}	Case reports	Case reports	C

*For grading of recommendations and level of evidence see Appendix 1.

controls bleeding while allowing for portal decompression by preserving vessel patency.^{15,16} In a randomized trial of 54 patients, the intravariceal technique was superior to the paravariceal technique in acute hemostasis (91% vs 18.7%, absolute risk reduction [ARR] 0.72, number needed to treat [NNT] 1.4), and total variceal obliteration.¹⁷ It is important to note, however, that endoscopists may not be able to distinguish an intravariceal injection from a paravariceal injection. In one study that used radiographic confirmation, 44% of intended intravariceal injections were actually paravariceal.¹⁸ In a recent study, EUS-guided sclerotherapy targeted at collateral veins was compared with standard intravariceal sclerotherapy with 2.5% ethanolamine. Of 50 randomized patients, there was a trend toward fewer variceal recurrences with the EUS-guided treatment (8% vs 17%), and the presence of collateral veins was associated with variceal recurrence ($P = .003$).¹⁹

Commonly used needles for injection generally include 23-gauge to 25-gauge needles that are no longer than 5 mm from the catheter tip. Longer needles are associated with an increased risk of bacteremia.²⁰ The freehand technique of using the flexible endoscope without an overtube is now more popular, in part, because the overtube has been associated with more complications.^{21,22} Intervals between sclerotherapy sessions to obliterate varices vary. Commonly reported frequencies range from 1 to 3 weeks, for an average of 3 to 6 sessions. More frequent intervals are associated with less rebleeding and faster eradication of varices but more mucosal ulceration.^{23,24} Finally, there is no current standard concentration for each sclerosant that would provide the lowest rebleeding rate concur-

rently with the lowest ulceration rate. In many ways, endoscopic injection sclerotherapy is a highly individualized technique, which, in turn, likely explains the variable results noted in the treatment of esophageal varices.

Sclerosants are not recommended for the primary prophylaxis of esophageal varices. Although there are many randomized-controlled trials to support prophylactic sclerotherapy, the results are variable.²⁵⁻³⁸ There are 3 meta-analyses of sclerotherapy for primary prophylaxis of bleeding. Because of significant heterogeneity between the trials included in these meta-analyses, it is not possible to reliably interpret the meta-analysis results.³⁹⁻⁴¹ One study, of 98 patients, was terminated early because of excess deaths in the treated group.⁴² Alternative treatments with fewer complications include beta-blockers and endoscopic variceal ligation.^{21,41}

Sclerosants are effective in controlling active variceal bleeding but are less favored than variceal ligation because of associated complications. Sclerotherapy can control acute variceal bleeding in 70% to 100% of cases.⁴¹ In more experienced hands, hemostasis can be achieved in more than 90% of cases.⁴ However, in a meta-analysis by Laine and Cook,⁹ endoscopic variceal ligation therapy significantly reduced rebleeding (odds ratio [OR] 0.52, 95% CI, 0.37-0.74), mortality (OR 0.67, 95% CI, 0.46-0.98), the frequency of esophageal strictures (OR 0.10, 95% CI, 0.03-0.29), and the number of sessions (2.2 fewer sessions, 95% CI, 0.9-3.5) required to achieve variceal obliteration when compared with injection sclerotherapy.

The combination of variceal ligation and injection sclerotherapy confers significant advantages when compared

with sclerotherapy alone, by decreasing complications, rebleeding, the number of sessions to achieve eradication, and variceal recurrence rates.⁴³⁻⁴⁶ Studies that compared combination therapy with variceal ligation alone did not find similar advantages.⁴⁷⁻⁵² Such studies suggest that variceal ligation alone is sufficient for the treatment of esophageal varices. However, sclerotherapy may play a role in treating small varices, and perhaps collateral veins, which are too small for ligation. In one study, varices were treated first by ligation until reduced to grade 2 and then were treated with injection sclerotherapy. This sequential combination of therapy demonstrated improved eradication rates and decreased mortality, rebleeding rates, and variceal recurrence rates.⁵³⁻⁵⁵ Pharmacologic therapy with vasoactive drugs, including octreotide and somatostatin, should be added to endoscopic therapy to improve control of active bleeding and to maintain short-term hemostasis.⁵⁶

After hemostasis is achieved in bleeding varices, the chance of rebleeding without further intervention ranges from 47% to 84% over a 1-year to 2-year period.⁴¹ Because of this, secondary prophylaxis to prevent rebleeding is indicated, and sclerotherapy can reduce rebleeding.⁵⁷⁻⁶¹ In a meta-analysis of 8 trials, sclerotherapy compared with no treatment significantly reduced rebleeding (OR 0.62, 95% CI, 0.49-0.79) and mortality (OR 0.77, 95% CI, 0.68-0.98). When compared with beta-blockers, sclerotherapy significantly reduced variceal rebleeding (OR 0.66, 95% CI, 0.50-0.88) but not mortality (OR 0.96, 95% CI, 0.71-1.28) in a meta-analysis of 9 trials.⁴¹ Another meta-analysis that compared sclerotherapy and beta-blockers reported similar results with a previous meta-analysis. In this analysis, sclerotherapy reduced rebleeding more than propranolol did, with an ARR of 0.17 (OR 0.5; 95% CI, 0.36-0.69) but had more adverse effects. When reported in the trials, the investigators calculated 113 adverse events with sclerotherapy compared with 52 with propranolol. Twenty-seven of the 113 events in the sclerotherapy group were considered severe versus 15 events in the propranolol group.⁶²

Rebleeding commonly occurs early after the initial bleeding episode and usually occurs before obliteration is achieved. Based on a meta-analysis of 2 trials, a combination of sclerotherapy and beta-blockers is superior to beta-blockers alone in reducing rebleeding (OR 0.49, 95% CI, 0.27-0.89) and mortality (OR 0.52, 95% CI, 0.28-0.95).⁴¹ Interestingly, studies that compared combination therapy with sclerotherapy alone have been mixed. The addition of propranolol to sclerotherapy was studied in several trials, and only 3 studies demonstrated a significant reduction in rebleeding, and no studies demonstrated an improvement in survival. In these 3 studies, the OR ranged from 0.11 to 0.41, with a 95% CI range of 0.03 to 0.99.⁶³⁻⁶⁵ Failure to appreciate a significant benefit with the addition of beta-blocker may be because of an inadequate lowering of the hepatic venous pressure gradient.⁶⁶ These results further support sclerotherapy as superior to beta-blockers in the secondary prophylaxis of esophageal variceal bleeding.

TABLE 2. Summary of complications of sclerotherapy associated with variceal bleeding

Complications of sclerotherapy

Immediate

- Substernal chest pain
- Low-grade fever
- Dysphagia
- Pleural effusion
- Chest radiographic changes

Delayed

- Mucosal ulceration
- Esophageal strictures
- Perforation
- Acute respiratory distress syndrome
- Pneumothorax
- Chylothorax
- Pericarditis
- Mediastinitis
- Fistulas
- Esophageal motility disorders
- Spinal-cord paralysis
- Mesenteric venous thrombosis
- Bacteremia

Endoscopic variceal ligation is preferred to sclerotherapy for the secondary prophylaxis of varices. Several trials compared the two techniques, and some trials found significantly less rebleeding (ARR 0.21-0.23, NNT 4.3-4.7) and fewer complications (ARR 0.20-0.33, NNT 3-5), and 1 trial showed a statistically significant improvement in survival (ARR 0.17, NNT 5.9) over a follow-up period of 10 to 27 months.⁶⁷⁻⁷⁰ The meta-analysis by Laine and Cook,⁹ mentioned earlier, also concluded that variceal ligation significantly reduced the rebleeding (OR 0.52, 95% CI, 0.37-0.74), the risk of stricture formation (OR 0.10, 95% CI, 0.03-0.29), and the mortality rate compared with sclerotherapy (OR 0.67, 95% CI, 0.46-0.98). Obliteration with sclerotherapy, however, is associated with a lower recurrence compared with endoscopic variceal ligation. In a study by de la Pena et al,⁷¹ variceal recurrence at 1 year was 47% and 23% (ARR 0.24, NNT 4.2) for variceal ligation and sclerotherapy, respectively. At 3 years, the recurrence rate was 92% and 55% (ARR 0.37, NNT 2.7), respectively.

Complications with sclerosants are an important reason why they are less popular (Table 2). Immediate complications are common, transient, and generally require no treatment. They include substernal chest pain, low-grade

fever, temporary dysphagia, pleural effusion, and nonspecific transient chest radiographic changes. The most common delayed complication is mucosal ulceration, which occurs in up to 90% of patients. Up to 20% of these ulcers can bleed.⁷² Other delayed and infrequent complications include esophageal strictures, perforation, acute respiratory distress syndrome, pneumothorax, chylothorax, pericarditis, mediastinitis, fistulas, pleural effusions, esophageal motility disorders, spinal cord paralysis, and mesenteric venous thrombosis.⁷³⁻⁷⁵ Transient bacteremia can occur in up to 35% of patients^{76,77}; antibiotic prophylaxis is thus recommended for patients with cardiac valvular disease and for those with ascites.⁷⁸

Tissue adhesives

Tissue adhesives, including cyanoacrylate-based glue, fibrin glue, and thrombin, have been used outside the United States for the treatment of variceal bleeding. At present, cyanoacrylate-based agents are not approved for endoscopic use by the U.S. Food and Drug Administration. Two versions of N-butyl-2-cyanoacrylate that have been studied for endoscopic use (Histoacryl [Braun, Melsungen, Germany] and Glubran [GEM S.r.l., Viareggio, Italy]) are available in Europe. Cyanoacrylate-based glue treats GI bleeding by polymerization of the liquid glue to a plastic cast, which occurs rapidly and independent of the coagulation cascade. To prevent damage to the endoscope, it has been recommended that silicone oil be applied to the tip of the endoscope. Cyanoacrylate should be mixed with lipiodol, an oily contrast agent, in a ratio of 1:1 to 1:1.5, to delay polymerization by approximately 20 seconds. Before injecting the mixture, lipiodol is injected first, through the catheter, to prevent adhesion. Because the viscosity of cyanoacrylate increases with lipiodol, rapid injection requires a Luer lock to connect the syringe to the injection catheter to prevent spraying. With a large bore (21-22 gauge) sclerotherapy needle, the bleeding site or vessel is punctured and 0.5 to 1.0 mL is administered and is rapidly followed by distilled water or normal saline solution to flush out any remaining cyanoacrylate in the injection catheter. Suctioning should be avoided for 20 seconds after injection to prevent cyanoacrylate adherence. A few weeks later, successful injection therapy will cause varix necrosis and extrusion of the solid plug from the lumen tract.^{5,79}

N-butyl-2-cyanoacrylate was studied in the treatment of esophageal varices in a few small randomized-controlled trials. When compared with various sclerosants, cyanoacrylate had an initial hemostasis rate of 84% to 100%, with the highest reported rebleeding rate of 28% over 30 days. In all 3 studies, cyanoacrylate performed equally to sclerosants, and one study demonstrated an absolute reduction in the in-hospital mortality rate of 39%.⁸⁰⁻⁸² The addition of cyanoacrylate to sclerosants in larger varices may also promote hemostasis, minimize rebleeding, and improve survival.⁸³⁻⁸⁵ The role for cyanoacrylate in

secondary and primary prophylaxis is unclear. In a randomized-controlled trial, cyanoacrylate was compared with propranolol for secondary prophylaxis. No differences in rebleeding or survival were observed, but more complications occurred in the cyanoacrylate-treated group.⁸⁶ The most common, and potentially fatal, complication is systemic embolization.^{74,79,87}

The use of fibrin glue in the treatment of bleeding esophageal varices is limited. In one small randomized-controlled trial, fibrin glue was compared with 1% polidocanol. Significantly less rebleeding, fewer complications, and increased survival over 28 days were observed in the fibrin glue-treated group.⁸⁸ The use of thrombin alone to treat esophageal varices has not been reported. Two studies evaluated thrombin as a "cocktail" combined with 1% sodium tetradecyl sulfate and cefazolin, and one study evaluated the addition of thrombin to 5% ethanolamine.⁸⁹⁻⁹¹ Although these studies suggest that the addition of thrombin is safe and effective, no further studies in the past 15 years have been reported.

Sclerosants remain the most studied injectable agents for the treatment and prevention of bleeding from esophageal varices. Although generally effective, the data are heterogeneous, because of various injectable solutions and techniques. Because of reduced complication rates, variceal banding ligation is considered the preferred first-line treatment. Yet, tissue adhesives offer a promising alternative and warrant further studies.

GASTRIC VARICES

Gastric varices are less common than esophageal varices but may be present in up to 20% of patients with portal hypertension, and 4% to 65% of gastric varices will bleed over 2 years.^{92,93} Variceal ligation has performed well in esophageal varices; however, results with gastric varices are not as favorable.⁹⁴ Bleeding is commonly more profound and difficult to control. Gastric varices exist in connection with esophageal varices as 2 types: GE varices type 1 (GOV1) are found in the lesser curvature, and GE varices type 2 (GOV2) are found in the cardia. Isolated gastric varices (IGV) exist as 2 types: IGV1 are located in the fundus, and IGV2 are sporadic. These distinctions are important in predicting the frequency of bleeding and the response to treatment.⁹²

Sclerosants

Compared with the experience with esophageal varices, sclerosants have had less success in the treatment of gastric varices,⁹⁵ because they are associated with a high incidence of complications, eg, gastric ulcerations and perforation, and recurrent bleeding rates of 37% to 53%.^{92,95} Sclerosants that were described in the treatment of gastric varices include 5% ethanolamine oleate, absolute ethanol, and 1% polidocanol.⁹⁶⁻⁹⁸ The use of sodium

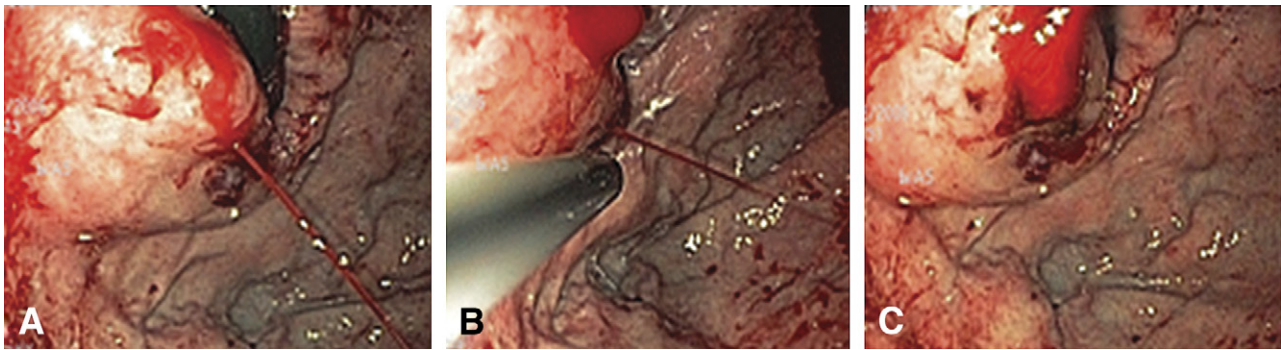


Figure 1. **A**, A spurting gastric varix in the gastric cardia of a 42-year-old man with hepatitis B–related cirrhosis. **B**, A total of 10 mL sodium morrhuate was injected at and around the bleeding site. **C**, The spurting hemorrhage ceased, and slow residual oozing remained. The patient subsequently had an interventional radiology evaluation, which showed no further bleeding.

morrhuate in the treatment of an active spurting gastric varix in the cardia is illustrated in Figure 1. In prospective studies, 5% ethanolamine had a hemostasis rate of 52% to 67%, a rebleeding rate of 25% to 43%, and a mortality rate of 67% over 1 year.^{96,99} Absolute ethanol was compared with cyanoacrylate in a small randomized-controlled trial of patients with isolated fundal varices. Although cyanoacrylate had a significantly higher rate of variceal obliteration (ARR 0.66, NNT 1.5), there was no significant difference in acute hemostasis. Ethanol controlled 62% (compared with 89% in cyanoacrylate) of bleeding varices and obliterated 44% of varices.¹⁰⁰ These results were similar to a previous case series of patients treated with ethanol. Ethanol controlled 66% of bleeding varices, and the obliteration rate varied according to the location of the varix: GOV1 and GOV2 had higher obliteration rates than fundal varices. Moreover, rebleeding was higher in the fundal varices.⁹⁸ Sclerotherapy is more successful with GOV than with IGV.^{95,98,101} In a case series of 56 patients, 1% polidocanol was studied in combination with variceal ligation.⁹⁷ In this study, this combination achieved 100% hemostasis, 100% obliteration of varices, and a rebleeding rate of 3.6%. Based on these results, the role of sclerotherapy in treating gastric varices is limited. Patients with GOV may have a higher chance of success with sclerotherapy than those patients with fundal varices.

Tissue adhesives

One of the first descriptions of the use of N-butyl-2-cyanoacrylate for the treatment of bleeding gastric varices was in 1987, when, in a series of 200 patients, Soehendra et al¹⁰² described reducing the mortality rate from 30% to 17% compared with historical controls. Through multiple case series, cyanoacrylate has had a hemostasis rate of 58% to 100% and a rebleeding rate of 0% to 40%.¹⁰³⁻¹⁰⁸ In one prospective randomized study of 60 patients, cyanoacrylate was significantly superior to band ligation in achieving initial hemostasis (ARR 0.42, NNT 2.4) and decreased rebleeding (ARR 0.23, NNT 4.3). However, rates of obliteration were similar.⁹⁴ In another prospective

study, of 38 patients, cyanoacrylate was significantly superior to 5% ethanolamine in hemostasis and the need for surgery but with no difference in survival.⁹⁹ As mentioned earlier in the use of ethanol for gastric varices, a prospective study of 37 patients that compared cyanoacrylate with ethanol, showed cyanoacrylate to have a significantly higher rate of variceal obliteration (ARR 0.66, NNT 1.5) in a significantly shorter period of time (mean \pm SD, 2.0 ± 1.6 weeks vs 4.7 ± 3.2 weeks; $P < .05$). Cyanoacrylate had a higher rate of hemostasis (89% vs 62%) but this was not significant.¹⁰⁰ Complications in the treatment of gastric varices with cyanoacrylate are similar to the experiences noted in the treatment of esophageal varices and peptic ulcers. Although not common with experienced physicians, major complications can arise; they entail early polymerization, which leads to needle adhesion to the varix, embolization, abscess formation, esophageal perforation, peritoneal cavity extravasation, and splenic infarction.^{94,109-114}

Because N-butyl-2-cyanoacrylate is not available in the United States, there is interest in studying the efficacy of an analog, 2-octyl-cyanoacrylate, (Dermabond; Ethicon, Somerville, NJ) for the treatment of gastric varices. Dermabond is approved in the United States for skin closure, but Rengstorff and Binmoeller¹¹⁵ reported its use in 25 patients with gastric varices. In 3 patients with actively bleeding varices, immediate hemostasis was achieved in 100%. The rebleeding rate was 4% over 11 months, and no significant procedure-related complications were noted.¹¹⁵ However, pulmonary embolization with Dermabond has been reported.¹¹⁶

Thrombin has been studied in the treatment of bleeding gastric varices. Compared with cyanoacrylate, thrombin is appealing, because it is technically simpler to administer and may have fewer complications. However, thrombin is expensive and includes the potential for the transmission of infection, particularly when bovine thrombin is used. The injection technique is similar to that described above for the treatment of bleeding ulcers. Williams et al¹¹⁷ injected 1000 units of bovine thrombin

in 11 patients with gastric varices by using the intravariceal method. Hemostasis was achieved in all 11 patients, with rebleeding experienced in only 1 patient over 9 months. Another case series of 52 patients had similar findings.¹¹⁸ Recently, in a case series of 12 patients with gastric varices who were treated with human thrombin, hemostasis was observed in 75% of the patients. The rebleeding rate was 25%, and there was 1 bleeding-related mortality, without any thrombin-related complications or adverse events observed.¹¹⁹

There are 2 case series on the use of fibrin glue for the treatment of gastric varices. In one series, of 15 patients treated with fibrin glue (Beriplast; Aventis Behring Ltd, Marburg, Germany), hemostasis was accomplished in 93% of patients, the rebleeding rate was 26%, and the 30-day mortality rate was 6.7%.¹²⁰ In the other series, of 10 patients, when using Beriplast, hemostasis was achieved in 70% of patients.¹²¹

There is a need for better endoscopic injection therapies for the treatment of gastric varices. Sclerosants have limited efficacy and appear best for patients who have GOV. Similar to esophageal varices, complications from sclerosant therapy is another limitation. Tissue adhesives, particularly cyanoacrylate-based glues, warrant further investigation.

RECTAL VARICES

Approximately 43% to 78% of patients with portal hypertension will have rectal varices seen during an endoscopy.^{122,123} Although bleeding from rectal varices is rare, it can be massive and fatal.¹²⁴ Currently, there is no standard treatment for rectal varices, and evidence to support the use of endoscopic injection therapies is limited to case reports. Four case reports of the use of sclerosants and 2 case reports on the use of N-butyl-2-cyanoacrylate demonstrated efficacy in treating rectal varices.¹²⁵⁻¹³⁰ Further studies are needed.

CONCLUSIONS

Injection therapy for bleeding variceal-related GI disorders can be safe and effective (Table 1, Appendix 2). In esophageal varices, sclerosants are effective but limited by several complications. Endoscopic variceal band ligation and nonendoscopic medical therapy are the favored initial treatments for bleeding esophageal varices. Tissue adhesives, particularly cyanoacrylate-based compounds, are effective but can be limited by complications as well. Sclerosants are less effective in the treatment of gastric varices than of esophageal varices, and tissue adhesives, particularly cyanoacrylate-based glue, appear to be more effective. However, cyanoacrylate-based glue is not yet approved for endoscopic use in the United States and has potentially serious complications. Further investigation of these compounds is needed, particularly for gastric

and rectal varices when sclerosant therapy is of limited benefit.

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DISCLOSURE

The authors report that there are no disclosures relevant to this publication.

Abbreviations: ARR, absolute risk reduction; GE, gastroesophageal; GOV, gastroesophageal varices type; GOV1, gastroesophageal varices type 1; GOV2, gastroesophageal varices type 2; IGV, isolated gastric varices; NNT, number needed to treat; OR, odds ratio.

REFERENCES

1. Church NI, Palmer K. Evidence based gastroenterology and hepatology. London: BMJ Books; 1999.
2. Silverstein FE, Gilbert DA, Tedesco FJ, et al. The national ASGE survey on upper gastrointestinal bleeding. I. Study design and baseline data. *Gastrointest Endosc* 1981;27:73-9.
3. Bornman PC, Krige JE, Terblanche J. Management of oesophageal varices. *Lancet* 1994;343:1079-84.
4. Helmy A, Hayes PC. Review article: current endoscopic therapeutic options in the management of variceal bleeding. *Aliment Pharmacol Ther* 2001;15:575-94.
5. Memon MA, Jones WF. Injection therapy for variceal bleeding. *Gastrointest Endosc Clin N Am* 1999;9:231-52.
6. Desai CS, Shah SR, Mathur SK. Emergency sclerotherapy for control of acute oesophageal variceal bleeding using 3% aqueous phenol: a 15-year experience. *ANZ J Surg* 2004;74:460-2.
7. Clark AW, Macdougall BR, Westaby D, et al. Prospective controlled trial of injection sclerotherapy in patient with cirrhosis and recent variceal haemorrhage. *Lancet* 1980;ii:552-4.
8. Macdougall BR, Westaby D, Theodossi A, et al. Increased long-term survival in variceal haemorrhage using injection sclerotherapy. Results of a controlled trial. *Lancet* 1982;i:124-7.
9. Laine L, Cook D. Endoscopic ligation compared with sclerotherapy for treatment of esophageal variceal bleeding. A meta-analysis. *Ann Intern Med* 1995;123:280-7.
10. Chang KY, Wu CS, Chen PC. Prospective, randomized trial of hypertonic glucose water and sodium tetradecyl sulfate for gastric variceal bleeding in patients with advanced liver cirrhosis. *Endoscopy* 1996; 28:481-6.
11. Chan AC, Chung SC, Sung JY, et al. A double-blind randomized controlled trial comparing sodium tetradecyl sulphate and ethanolamine oleate in the sclerotherapy of bleeding oesophageal varices. *Endoscopy* 1993;25:513-7.
12. Kochhar R, Goenka MK, Mehta S, et al. A comparative evaluation of sclerosants for esophageal varices: a prospective randomized controlled study. *Gastrointest Endosc* 1990;36:127-30.
13. Kitano S, Wada H, Yamaga H, et al. Comparative effects of 5% ethanolamine oleate versus 5% sodium morrhuate for sclerotherapy of oesophageal varices. *J Gastroenterol Hepatol* 1991;6:476-80.
14. Ferrari AP, de Paulo GA, de Macedo CM, et al. Efficacy of absolute alcohol injection compared with band ligation in the eradication of esophageal varices. *Arq Gastroenterol* 2005;42:72-6.

15. Paoluzi P, Pietroiusti A, Ferrari S, et al. Absolute alcohol in esophageal vein sclerosis. *Gastrointest Endosc* 1988;34:400-2.
16. Paquet KJ. Endoscopic paravariceal injection sclerotherapy of the esophagus—indications, technique, complications: results of a period of 14 years. *Gastrointest Endosc* 1983;29:310-5.
17. Sarin SK, Nanda R, Sachdev G, et al. Intravariceal versus paravariceal sclerotherapy: a prospective, controlled, randomised trial. *Gut* 1987; 28:657-62.
18. Waring JP, Sanowski RA, Pardy K, et al. Does the addition of methylene blue to the sclerosant improve the accuracy of injections during variceal sclerotherapy? *Gastrointest Endosc* 1991;37:159-60.
19. de Paulo GA, Ardengh JC, Nakao FS, et al. Treatment of esophageal varices: a randomized controlled trial comparing endoscopic sclerotherapy and EUS-guided sclerotherapy of esophageal collateral veins. *Gastrointest Endosc* 2006;63:396-402;quiz 463.
20. Snady H, Korsten MA, Wayne JD. The relationship of bacteremia to the length of injection needle in endoscopic variceal sclerotherapy. *Gastrointest Endosc* 1985;31:243-6.
21. Krige JE, Shaw JM, Bornman PC. The evolving role of endoscopic treatment for bleeding esophageal varices. *World J Surg* 2005;29: 966-73.
22. Westaby D, Macdougall BR, Melia W, et al. A prospective randomized study of two sclerotherapy techniques for esophageal varices. *Hepatology* 1983;3:681-4.
23. Westaby D, Melia WM, Macdougall BR, et al. Injection sclerotherapy for oesophageal varices: a prospective randomised trial of different treatment schedules. *Gut* 1984;25:129-32.
24. Sarin SK, Sachdev G, Nanda R, et al. Comparison of the two time schedules for endoscopic sclerotherapy: a prospective randomised controlled study. *Gut* 1986;27:710-3.
25. Andreani T, Poupon RE, Balkau BJ, et al. Preventive therapy of first gastrointestinal bleeding in patients with cirrhosis: results of a controlled trial comparing propranolol, endoscopic sclerotherapy and placebo. *Hepatology* 1990;12:1413-9.
26. Prophylaxis of first hemorrhage from esophageal varices by sclerotherapy, propranolol or both in cirrhotic patients: a randomized multicenter trial. The PROVA Study Group. *Hepatology* 1991;14: 1016-24.
27. Paquet KJ. Prophylactic endoscopic sclerosing treatment of the esophageal wall in varices: a prospective controlled randomized trial. *Endoscopy* 1982;14:4-5.
28. Witzel L, Wolbergs E, Merki H. Prophylactic endoscopic sclerotherapy of oesophageal varices. A prospective controlled study. *Lancet* 1985; i:773-5.
29. Koch H, Henning H, Grimm H, et al. Prophylactic sclerosing of esophageal varices: results of a prospective controlled study. *Endoscopy* 1986;18:40-3.
30. Kobe E, Zipprich B, Schentke KU, et al. Prophylactic endoscopic sclerotherapy of esophageal varices: a prospective randomized trial. *Endoscopy* 1990;22:245-8.
31. Santangelo WC, Dueno MI, Estes BL, et al. Prophylactic sclerotherapy of large esophageal varices. *N Engl J Med* 1988;318:814-8.
32. Sauerbruch T, Wotzka R, Kopcke W, et al. Prophylactic sclerotherapy before the first episode of variceal hemorrhage in patients with cirrhosis. *N Engl J Med* 1988;319:8-15.
33. Piai G, Cipolletta L, Claar M, et al. Prophylactic sclerotherapy of high-risk esophageal varices: results of a multicentric prospective controlled trial. *Hepatology* 1988;8:1495-500.
34. Potzi R, Bauer P, Reichel W, et al. Prophylactic endoscopic sclerotherapy of oesophageal varices in liver cirrhosis. A multicentre prospective controlled randomised trial in Vienna. *Gut* 1989;30:873-9.
35. Russo A, Giannone G, Magnano A, et al. Prophylactic sclerotherapy in nonalcoholic liver cirrhosis: preliminary results of a prospective controlled randomized trial. *World J Surg* 1989;13:149-53.
36. Triger DR, Smart HL, Hosking SW, et al. Prophylactic sclerotherapy for esophageal varices: long-term results of a single-center trial. *Hepatology* 1991;13:117-23.
37. Prophylactic sclerotherapy for esophageal varices in men with alcoholic liver disease. A randomized, single-blind, multicenter clinical trial. The Veterans Affairs Cooperative Variceal Sclerotherapy Group. *N Engl J Med* 1991;324:1779-84.
38. De Franchis R, Primignani M, Arcidiacono PG, et al. Prophylactic sclerotherapy in high-risk cirrhotics selected by endoscopic criteria. A multicenter randomized controlled trial. *Gastroenterology* 1991;101: 1087-93.
39. Pagliaro L, D'Amico G, Sorensen TI, et al. Prevention of first bleeding in cirrhosis. A meta-analysis of randomized trials of nonsurgical treatment. *Ann Intern Med* 1992;117:59-70.
40. Fardy JM, Laupacis A. A meta-analysis of prophylactic endoscopic sclerotherapy for esophageal varices. *Am J Gastroenterol* 1994;89: 1938-48.
41. D'Amico G, Pagliaro L, Bosch J. The treatment of portal hypertension: a meta-analytic review. *Hepatology* 1995;22:332-54.
42. Snady H. The role of sclerotherapy in the treatment of esophageal varices: personal experience and a review of randomized trials. *Am J Gastroenterol* 1987;82:813-22.
43. Garg PK, Joshi YK, Tandon RK. Comparison of endoscopic variceal sclerotherapy with sequential endoscopic band ligation plus low-dose sclerotherapy for secondary prophylaxis of variceal hemorrhage: a prospective randomized study. *Gastrointest Endosc* 1999;50:369-73.
44. Shigemitsu T, Yoshida T, Harada T, et al. Endoscopic injection sclerotherapy with ligation versus endoscopic injection sclerotherapy alone in the management of esophageal varices: a prospective randomized trial. *Hepatogastroenterology* 2000;47:733-7.
45. Nishikawa Y, Hosokawa Y, Doi T, et al. Evaluation of endoscopic injection sclerotherapy with and without simultaneous ligation for the treatment of esophageal varices. *J Gastroenterol* 1999;34:159-62.
46. Hou MC, Chen WC, Lin HC, et al. A new "sandwich" method of combined endoscopic variceal ligation and sclerotherapy versus ligation alone in the treatment of esophageal variceal bleeding: a randomized trial. *Gastrointest Endosc* 2001;53:572-8.
47. Laine L, Stein C, Sharma V. Randomized comparison of ligation versus ligation plus sclerotherapy in patients with bleeding esophageal varices. *Gastroenterology* 1996;110:529-33.
48. Saeed ZA, Stiegmann GV, Ramirez FC, et al. Endoscopic variceal ligation is superior to combined ligation and sclerotherapy for esophageal varices: a multicenter prospective randomized trial. *Hepatology* 1997;25: 71-4.
49. Umehara M, Onda M, Tajiri T, et al. Sclerotherapy plus ligation versus ligation for the treatment of esophageal varices: a prospective randomized study. *Gastrointest Endosc* 1999;50:7-12.
50. Al Traif I, Fachartz FS, Al Jumah A, et al. Randomized trial of ligation versus combined ligation and sclerotherapy for bleeding esophageal varices. *Gastrointest Endosc* 1999;50:1-6.
51. Djurdjevic D, Janosevic S, Dapcevic B, et al. Combined ligation and sclerotherapy versus ligation alone for eradication of bleeding esophageal varices: a randomized and prospective trial. *Endoscopy* 1999;31:286-90.
52. Karsan HA, Morton SC, Shekelle PG, et al. Combination endoscopic band ligation and sclerotherapy compared with endoscopic band ligation alone for the secondary prophylaxis of esophageal variceal hemorrhage: a meta-analysis. *Dig Dis Sci* 2005;50:399-406.
53. Bhargava DK, Pokharna R. Endoscopic variceal ligation versus endoscopic variceal ligation and endoscopic sclerotherapy: a prospective randomized study. *Am J Gastroenterol* 1997;92:950-3.
54. Lo GH, Lai KH, Cheng JS, et al. The additive effect of sclerotherapy to patients receiving repeated endoscopic variceal ligation: a prospective, randomized, controlled trial. *Hepatology* 1998;28:391-5.
55. Seewald S, Seitz U, Yang AM, et al. Variceal bleeding and portal hypertension: still a therapeutic challenge? *Endoscopy* 2001;33: 126-39.
56. Banares R, Albillos A, Rincon D, et al. Endoscopic treatment versus endoscopic plus pharmacologic treatment for acute variceal bleeding: a meta-analysis. *Hepatology* 2002;35:609-15.

57. Sclerotherapy for male alcoholic cirrhotic patients who have bled from esophageal varices: results of a randomized, multicenter clinical trial. The Veterans Affairs Cooperative Variceal Sclerotherapy Group. *Hepatology* 1994;20:618-25.
58. Korula J, Balart LA, Radvan G, et al. A prospective, randomized controlled trial of chronic esophageal variceal sclerotherapy. *Hepatology* 1985;5:584-9.
59. Rossi V, Cales P, Burtin P, et al. Prevention of recurrent variceal bleeding in alcoholic cirrhotic patients: prospective controlled trial of propranolol and sclerotherapy. *J Hepatol* 1991;12:283-9.
60. Terblanche J, Bornman PC, Kahn D, et al. Failure of repeated injection sclerotherapy to improve long-term survival after oesophageal variceal bleeding. A five-year prospective controlled clinical trial. *Lancet* 1983;ii:1328-32.
61. Sclerotherapy after first variceal hemorrhage in cirrhosis. A randomized multicenter trial. The Copenhagen Esophageal Varices Sclerotherapy Project. *N Engl J Med* 1984;311:1594-600.
62. Bernard B, Lebrech D, Mathurin P, et al. Propranolol and sclerotherapy in the prevention of gastrointestinal rebleeding in patients with cirrhosis: a meta-analysis. *J Hepatol* 1997;26:312-24.
63. Jensen LS, Krarup N. Propranolol in prevention of rebleeding from esophageal varices during the course of endoscopic sclerotherapy. *Scand J Gastroenterol* 1989;24:339-45.
64. Vinel JP, Lamouliatte H, Cales P, et al. Propranolol reduces the rebleeding rate during endoscopic sclerotherapy before variceal obliteration. *Gastroenterology* 1992;102:1760-3.
65. Avgerinos A, Rekoumis G, Klonis C, et al. Propranolol in the prevention of recurrent upper gastrointestinal bleeding in patients with cirrhosis undergoing endoscopic sclerotherapy. A randomized controlled trial. *J Hepatol* 1993;19:301-11.
66. Villanueva C, Balanzo J, Novella MT, et al. Nadolol plus isosorbide mononitrate compared with sclerotherapy for the prevention of variceal rebleeding. *N Engl J Med* 1996;334:1624-9.
67. Gimson AE, Ramage JK, Panos MZ, et al. Randomised trial of variceal banding ligation versus injection sclerotherapy for bleeding esophageal varices. *Lancet* 1993;342:391-4.
68. Laine L, el-Newihi HM, Migikovsky B, et al. Endoscopic ligation compared with sclerotherapy for the treatment of bleeding esophageal varices. *Ann Intern Med* 1993;119:1-7.
69. Stiegmann GV, Goff JS, Michaletz-Onody PA, et al. Endoscopic sclerotherapy as compared with endoscopic ligation for bleeding esophageal varices. *N Engl J Med* 1992;326:1527-32.
70. Avgerinos A, Armonis A, Manolakopoulos S, et al. Endoscopic sclerotherapy versus variceal ligation in the long-term management of patients with cirrhosis after variceal bleeding. A prospective randomized study. *J Hepatol* 1997;26:1034-41.
71. de la Pena J, Rivero M, Sanchez E, et al. Variceal ligation compared with endoscopic sclerotherapy for variceal hemorrhage: prospective randomized trial. *Gastrointest Endosc* 1999;49:417-23.
72. Schuman BM, Beckman JW, Tedesco FJ, et al. Complications of endoscopic injection sclerotherapy: a review. *Am J Gastroenterol* 1987;82:823-30.
73. Truesdale RA Jr, Wong RK. Complications of esophageal variceal sclerotherapy. *Gastroenterol Clin North Am* 1991;20:859-70.
74. Krige JE, Bornman PC, Shaw JM, et al. Complications of endoscopic variceal therapy. *S Afr J Surg* 2005;43:177-88:190-4.
75. Lee JG, Lieberman DA. Complications related to endoscopic hemostasis techniques. *Gastrointest Endosc Clin N Am* 1996;6:305-21.
76. Rolando N, Gimson A, Philpott-Howard J, et al. Infectious sequelae after endoscopic sclerotherapy of esophageal varices: role of antibiotic prophylaxis. *J Hepatol* 1993;18:290-4.
77. Selby WS, Norton ID, Pokorny CS, et al. Bacteremia and bacterascites after endoscopic sclerotherapy for bleeding esophageal varices and prevention by intravenous cefotaxime: a randomized trial. *Gastrointest Endosc* 1994;40:680-4.
78. Hirota WK, Petersen K, Baron TH, et al. Guidelines for antibiotic prophylaxis for GI endoscopy. *Gastrointest Endosc* 2003;58:475-82.
79. Petersen B, Barkun A, Carpenter S, et al. Tissue adhesives and fibrin glues. *Gastrointest Endosc* 2004;60:327-33.
80. Maluf-Filho F, Sakai P, Ishioka S, et al. Endoscopic sclerosis versus cyanoacrylate endoscopic injection for the first episode of variceal bleeding: a prospective, controlled, and randomized study in Child-Pugh class C patients. *Endoscopy* 2001;33:421-7.
81. Sung JJ, Yeo W, Suen R, et al. Injection sclerotherapy for variceal bleeding in patients with hepatocellular carcinoma: cyanoacrylate versus sodium tetradecyl sulphate. *Gastrointest Endosc* 1998;47:235-9.
82. Omar MM, Fakhry SM, Mostafa I. Immediate endoscopic injection therapy of bleeding esophageal varices: a prospective comparative evaluation of injecting materials in Egyptian patients with portal hypertension. *J Egypt Soc Parasitol* 1998;28:159-68.
83. Feretis C, Dimopoulos C, Benakis P, et al. N-butyl-2-cyanoacrylate (Histoacryl) plus sclerotherapy versus sclerotherapy alone in the treatment of bleeding esophageal varices: a randomized prospective study. *Endoscopy* 1995;27:355-7.
84. Thakeb F, Salama Z, Salama H, et al. The value of combined use of N-butyl-2-cyanoacrylate and ethanolamine oleate in the management of bleeding esophagogastric varices. *Endoscopy* 1995;27:358-64.
85. Lux G, Retterspitz M, Stabenow-Lohbauer U, et al. Treatment of bleeding esophageal varices with cyanoacrylate and polidocanol, or polidocanol alone: results of a prospective study in an unselected group of patients with cirrhosis of the liver. *Endoscopy* 1997;29:241-6.
86. Evrard S, Dumonceau JM, Delhay M, et al. Endoscopic Histoacryl obliteration vs. propranolol in the prevention of esophagogastric variceal rebleeding: a randomized trial. *Endoscopy* 2003;35:729-35.
87. Seewald S, Sriram PV, Naga M, et al. Cyanoacrylate glue in gastric variceal bleeding. *Endoscopy* 2002;34:926-32.
88. Zimmer T, Rucktaschel F, Stolzel U, et al. Endoscopic sclerotherapy with fibrin glue as compared with polidocanol to prevent early esophageal variceal rebleeding. *J Hepatol* 1998;28:292-7.
89. Nakamura R, Bucci LA, Sugawa C, et al. Sclerotherapy of bleeding esophageal varices using a thrombogenic cocktail. *Am Surg* 1991;57:226-30.
90. Kitano S, Hashizume M, Yamaga H, et al. Human thrombin plus 5 per cent ethanolamine oleate injected to sclerose esophageal varices: a prospective randomized trial. *Br J Surg* 1989;76:715-8.
91. Lyons SD, Sugawa C, Geller ER, et al. Comparison of 1% sodium tetradecyl sulfate to a thrombogenic sclerosant cocktail for endoscopic sclerotherapy. *Am Surg* 1988;54:81-4.
92. Sarin SK, Lahoti D, Saxena SP, et al. Prevalence, classification and natural history of gastric varices: a long-term follow-up study in 568 portal hypertension patients. *Hepatology* 1992;16:1343-9.
93. Northup PG, Caldwell SH. Treatment of bleeding gastric varices. *J Gastroenterol Hepatol* 2005;20:1631-3.
94. Lo GH, Lai KH, Cheng JS, et al. A prospective, randomized trial of butyl cyanoacrylate injection versus band ligation in the management of bleeding gastric varices. *Hepatology* 2001;33:1060-4.
95. Trudeau W, Prindiville T. Endoscopic injection sclerosis in bleeding gastric varices. *Gastrointest Endosc* 1986;32:264-8.
96. Oho K, Iwao T, Sumino M, et al. Ethanolamine oleate versus butyl cyanoacrylate for bleeding gastric varices: a nonrandomized study. *Endoscopy* 1995;27:349-54.
97. Arakaki Y, Murakami K, Takahashi K, et al. Clinical evaluation of combined endoscopic variceal ligation and sclerotherapy of gastric varices in liver cirrhosis. *Endoscopy* 2003;35:940-5.
98. Sarin SK. Long-term follow-up of gastric variceal sclerotherapy: an eleven-year experience. *Gastrointest Endosc* 1997;46:8-14.

99. Ogawa K, Ishikawa S, Naritaka Y, et al. Clinical evaluation of endoscopic injection sclerotherapy using n-butyl-2-cyanoacrylate for gastric variceal bleeding. *J Gastroenterol Hepatol* 1999;14:245-50.
100. Sarin SK, Jain AK, Jain M, et al. A randomized controlled trial of cyanoacrylate versus alcohol injection in patients with isolated fundic varices. *Am J Gastroenterol* 2002;97:1010-5.
101. Gimson AE, Westaby D, Williams R. Endoscopic sclerotherapy in the management of gastric variceal haemorrhage. *J Hepatol* 1991;13:274-8.
102. Soehendra N, Grimm H, Nam VC, et al. N-butyl-2-cyanoacrylate: a supplement to endoscopic sclerotherapy. *Endoscopy* 1987;19:221-4.
103. Huang YH, Yeh HZ, Chen GH, et al. Endoscopic treatment of bleeding gastric varices by N-butyl-2-cyanoacrylate (Histoacryl) injection: long-term efficacy and safety. *Gastrointest Endosc* 2000;52:160-7.
104. Lee YT, Chan FK, Ng EK, et al. EUS-guided injection of cyanoacrylate for bleeding gastric varices. *Gastrointest Endosc* 2000;52:168-74.
105. Dhiman RK, Chawla Y, Taneja S, et al. Endoscopic sclerotherapy of gastric variceal bleeding with N-butyl-2-cyanoacrylate. *J Clin Gastroenterol* 2002;35:222-7.
106. Noophun P, Kongkam P, Gonlachanvit S, et al. Bleeding gastric varices: results of endoscopic injection with cyanoacrylate at King Chulalongkorn Memorial Hospital. *World J Gastroenterol* 2005;11:7531-5.
107. Akahoshi T, Hashizume M, Shimabukuro R, et al. Long-term results of endoscopic Histoacryl injection sclerotherapy for gastric variceal bleeding: a 10-year experience. *Surgery* 2002;131:S176-81.
108. Mostafa I, Omar MM, Nouh A. Endoscopic control of gastric variceal bleeding with butyl cyanoacrylate in patients with schistosomiasis. *J Egypt Soc Parasitol* 1997;27:405-10.
109. Chen WC, Hou MC, Lin HC, et al. Bacteremia after endoscopic injection of N-butyl-2-cyanoacrylate for gastric variceal bleeding. *Gastrointest Endosc* 2001;54:214-8.
110. Bhasin DK, Sharma BC, Prasad H, et al. Endoscopic removal of sclerotherapy needle from gastric varix after N-butyl-2-cyanoacrylate injection. *Gastrointest Endosc* 2000;51:497-8.
111. Wai CT, Sutedja DS, Khor CJ, et al. Esophageal sinus formation as a complication of cyanoacrylate injection. *Gastrointest Endosc* 2005;61:773-5.
112. Hwang SS, Kim HH, Park SH, et al. N-butyl-2-cyanoacrylate pulmonary embolism after endoscopic injection sclerotherapy for gastric variceal bleeding. *J Comput Assist Tomogr* 2001;25:16-22.
113. Cheng HC, Cheng PN, Tsai YM, et al. Sclerosant extravasation as a complication of sclerosing endotherapy for bleeding gastric varices. *Endoscopy* 2004;36:239-41.
114. Cheng PN, Sheu BS, Chen CY, et al. Splenic infarction after Histoacryl injection for bleeding gastric varices. *Gastrointest Endosc* 1998;48:426-7.
115. Rengstorff DS, Binmoeller KF. A pilot study of 2-octyl cyanoacrylate injection for treatment of gastric fundal varices in humans. *Gastrointest Endosc* 2004;59:553-8.
116. Rickman OB, Utz JP, Aughenbaugh GL, et al. Pulmonary embolization of 2-octyl cyanoacrylate after endoscopic injection therapy for gastric variceal bleeding. *Mayo Clin Proc* 2004;79:1455-8.
117. Williams SG, Peters RA, Westaby D. Thrombin: an effective treatment for gastric variceal haemorrhage. *Gut* 1994;35:1287-9.
118. Przemioslo RT, McNair A, Williams R. Thrombin is effective in arresting bleeding from gastric variceal hemorrhage. *Dig Dis Sci* 1999;44:778-81.
119. Yang WL, Tripathi D, Therapondos G, et al. Endoscopic use of human thrombin in bleeding gastric varices. *Am J Gastroenterol* 2002;97:1381-5.
120. Datta D, Vlavianos P, Alisa A, et al. Use of fibrin glue (Beriplast) in the management of bleeding gastric varices. *Endoscopy* 2003;35:675-8.
121. Heneghan MA, Byrne A, Harrison PM. An open pilot study of the effects of a human fibrin glue for endoscopic treatment of patients with acute bleeding from gastric varices. *Gastrointest Endosc* 2002;56:422-6.
122. Chawla Y, Dilawari JB. Anorectal varices: their frequency in cirrhotic and non-cirrhotic portal hypertension. *Gut* 1991;32:309-11.
123. Dhiman RK, Saraswat VA, Choudhuri G, et al. Endosonographic, endoscopic, and histologic evaluation of alterations in the rectal venous system in patients with portal hypertension. *Gastrointest Endosc* 1999;49:218-27.
124. Bresci G, Gambardella L, Parisi G, et al. Colonic disease in cirrhotic patients with portal hypertension: an endoscopic and clinical evaluation. *J Clin Gastroenterol* 1998;26:222-7.
125. Ikeda K, Konishi Y, Nakamura T, et al. Rectal varices successfully treated by endoscopic injection sclerotherapy after careful hemodynamic evaluation: a case report. *Gastrointest Endosc* 2001;54:788-91.
126. Yamanaka T, Shiraki K, Ito T, et al. Endoscopic sclerotherapy (ethanolamine oleate injection) for acute rectal varices bleeding in a patient with liver cirrhosis. *Hepatogastroenterology* 2002;49:941-3.
127. Wang M, Desigan G, Dunn D. Endoscopic sclerotherapy for bleeding rectal varices: a case report. *Am J Gastroenterol* 1985;80:779-80.
128. Weiserbs DB, Zfass AM, Messmer J. Control of massive hemorrhage from rectal varices with sclerotherapy. *Gastrointest Endosc* 1986;32:419-21.
129. Chen WC, Hou MC, Lin HC, et al. An endoscopic injection with N-butyl-2-cyanoacrylate used for colonic variceal bleeding: a case report and review of the literature. *Am J Gastroenterol* 2000;95:540-2.
130. Ryu SH, Moon JS, Kim I, et al. Endoscopic injection sclerotherapy with N-butyl-2-cyanoacrylate in a patient with massive rectal variceal bleeding: a case report. *Gastrointest Endosc* 2005;62:632-5.

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APPENDIX 1

Grading of recommendations and level of evidence*

Grade A

- Evidence from large randomized clinical trials (RCT) or systematic reviews (including meta-analyses) of multiple randomized trials, which collectively have at least as much data as a single well-defined trial.
- Evidence from at least one “all or none” high-quality cohort study; in which all patients died/failed with conventional therapy and some survived/succeeded with the new therapy (eg, chemotherapy for tuberculosis, meningitis, or defibrillation for ventricular fibrillation); or in which many died/failed with conventional therapy and none died/failed with the new therapy (eg, penicillin for pneumococcal infections).
- Evidence from at least one moderate-sized RCT or meta-analysis of small trials, which collectively only has a moderate number of patients.
- Evidence from at least one RCT.

Grade B

- Evidence from at least one high-quality study of nonrandomized cohorts who did and did not receive the new therapy.
- Evidence from at least one high-quality case control study.
- Evidence from at least one high-quality case series.

Grade C

- Opinions from experts, without reference or access to any of the foregoing (eg, argument from physiology, bench research, or first principles).

*From Ref. 1.

APPENDIX 2

General instructions for commonly used injection techniques for variceal-related GI bleeding

1. Sclerosants (1% polidocanol, 5% ethanolamine oleate, 3% sodium tetradecyl sulfate, sodium morrhuate, and 3% phenol)
 - Indication: Esophageal varices
 - Gastric varices
 - Rectal varices
 - For variceal bleeding:
 - a) Choose premade dilution of preferred sclerosant.
 - b) Inject with standard disposable injection needle (21-25 gauge) no longer than 5 mm.
 - Intravariceal technique: (esophageal)
 - i) Inject 1 to 2 mL directly into varix 1 cm below bleeding site.
 - ii) Inject 1 to 2 mL into all visible varices at the GE junction.
 - iii) Inject proximally in 3-cm to 5-cm intervals, up to 10 cm from GE junction.
 - iv) Approximately 10 to 20 mL is used per session based on size/number of varices.
 - Paravariceal technique: (esophageal)
 - i) Inject 1 to 2 mL in the submucosa adjacent to visible varices at the GE junction.
 - ii) Inject proximally up to 20 to 50 times, up to 10 cm from the GE junction.
 - c) Intervals between sessions range from 1 to 3 weeks for 3 to 6 sessions.
 - d) In the treatment of gastric and rectal varices, larger amounts (up to 10 mL) of sclerosants may be required to obliterate varices. Caution is recommended, because larger volumes of sclerosants are associated with more complications.

(continued on next page)

APPENDIX 2 (continued)

2. Ethanol

Indication: Esophageal varices

Gastric varices

For variceal bleeding:

- a) Inject with standard disposable injection needle (21-25 gauge).
- b) Follow intravariceal/paravariceal technique injecting 0.1-mL to 0.2-mL aliquots.
- c) Limit ethanol to 4 mL per session to minimize complications.

3. Thrombin

Indication: Gastric varices

- a) Bovine thrombin is delivered as dry powder vial that can be reconstituted with distilled water into 3.5 mL of 1000 international units. Human thrombin can be obtained locally through a blood bank or commercially.
- b) Inject with standard disposable injection needle (21-25 gauge)
- c) Inject 1-mL aliquots directly into the bleeding varix.

4. Fibrin glue

Commercial products:

Tisseel (Baxter, Westlake Village, Calif)

Hemaseel (Hemacure, Sarasota, Fla)

Beriplast (Aventis Behring Ltd, Marburg, Germany),

Indication: Esophageal varices

Gastric varices

- a) Double-lumen injection needle is recommended to prevent mixing of fibrinogen and thrombin to prevent premature fibrogenesis.
- b) Inject 1-mL aliquots of each substrate 2 to 3 mm from the bleeding site in 4 quadrants in nonvariceal bleeding and directly into the varix in variceal bleeding.
- c) If a double-lumen needle not available, then flush a standard injection needle with 1 mL of saline solution before and after injection of fibrinogen and thrombin.

5. N-butyl-2-cyanoacrylate

Commercial products:

Histoacryl (Braun, Melsungen, Germany)

Glubran (GEM S.r.l., Viareggio, Italy)

Not available in the United States

Indication: Esophageal varices

Gastric varices

Rectal varices

- a) Apply silicone oil to tip of the endoscope and suction through the working channel.
- b) Premix cyanoacrylate with lipiodol in a ratio of 1:1 to 1:1.5 to delay polymerization by approximately 20 seconds.
- c) Inject (with a 21-gauge to 22-gauge needle) lipiodol through the catheter before injecting the cyanoacrylate mixture.
- d) Inject by using a Luer lock to prevent spraying of mixture.
- e) Inject 0.5 to 1.0 mL of mixture through a large-bore injection needle at the bleeding site or into the vessel.
- f) Immediately inject distilled water or normal saline solution to flush any remaining cyanoacrylate in the injection catheter.
- g) Avoid suctioning for 20 seconds after injection to prevent endoscope damage.
- h) Success will cause varix necrosis and extrusion of the solid plug from the lumen tract a few weeks later.