

Cyanoacrylate applications in the GI tract

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Since their discovery in 1942 in the Eastman Kodak laboratory, cyanoacrylate polymers ("glue") have been widely studied and clinically applied as tissue adhesives. They have been used extensively in Europe since the 1970s for a variety of surgical applications including middle ear surgery, bone and cartilage grafts, repair of cerebrospinal fluid leaks, and skin closure. Interventional radiologists have used the polymers for embolization of aneurysms, arteriovenous malformations, fistulas, and vascular lacerations. This review will discuss the uses of glue for applications in the GI tract.

Cyanoacrylate glues: chemistry and properties

Cyanoacrylates are a class of synthetic glues applied as monomers, which polymerize in an exothermic reaction when in contact with a weak base such as blood.¹ They differ primarily in the length of their alkyl groups, which alter their physicochemical properties as described in the following. Two forms of glue are currently used in GI endoscopy (Fig. 1). N-butyl 2-cyanoacrylate (enbucrilate) has a 4-carbon alkyl group and is marketed as Indermil (Covidien, Mansfield, MA) and Histoacryl (B. Braun Medical, Bethlehem, PA). This has replaced the earlier 4-carbon isobutyl 2-cyanoacrylate (bucrylate). Ocrylate (2-octyl cyanoacrylate) has an 8-carbon alkyl group and is marketed as Dermabond (Johnson & Johnson, New Brunswick, NJ). Glubran 2 (GEM s.r.l., Viareggio, Italy) contains enbucrilate plus methacryloxy sulpholane, which increases polymerization time and reduces heat generation.²

A longer alkyl group slows polymerization and forms a polymer with lower tensile strength and greater flexibility.³ Cyanoacrylates degrade slowly in tissue, at a rate inversely proportional to the alkyl chain length, producing histotoxic compounds such as formaldehyde and cyanoacetate. These can cause a chronic foreign body reaction, with tissue necrosis and infection,⁴ which is less severe with a longer alkyl group.^{5,6} Although these issues are particularly associated with methyl and ethyl cyanoacrylates, en-

bucrilate has been shown to cause significant degenerative change in a rabbit aorta model⁵ and to cause significant inflammation in a lung resection model.⁷ Both enbucrilate and ocrylate caused inflammation and impaired tissue integration of mesh in an animal model of hernia repair.^{8,9}

GASTRIC VARICES

The application of glue in the treatment of gastric varices is now well-established. Percutaneous radiologic obliteration of gastric varices with glue was described by Lunderquist et al¹⁰ in 1978, and Soehendra et al¹¹ reported the first series of endoscopic treatment of gastric varices in 1986. Since then, a number of sizeable case series have demonstrated a hemostasis rate of >90%, variceal obliteration rates of 70% to 90%, and rebleeding rates <30%.^{12,13} The use of enbucrilate for bleeding gastric varices has been shown to be cost effective compared with medical treatment alone.¹⁴ Although rebleeding rates may be higher for enbucrilate injection versus transjugular intrahepatic portosystemic stent shunts,^{15,16} enbucrilate injection is more cost-effective in treating acute gastric variceal bleeding.¹⁷ As secondary prophylaxis, enbucrilate injection can reduce rebleeding rates as compared with band ligation¹⁸ and propranolol.¹⁹ As primary prophylaxis, enbucrilate has been shown to reduce the risk of bleeding and mortality from type 2 gastroesophageal varices (Sarin et al²⁰ for definitions) or type 1 isolated gastric varices >10 mm diameter as compared with propranolol alone.²¹

Most published experience on treatment of gastric varices has used enbucrilate. The rapid polymerization time of enbucrilate can result in premature solidification of the glue in the needle or entrapment of the needle within the varix.^{1,12,22} Damage to the endoscope also has been reported.²³ Enbucrilate is therefore usually diluted with lipiodol in ratios ranging from 1:1 to 1:1.6.¹ Lipiodol has the added property of allowing radiologic confirmation of injection and identification of embolization. Whereas glue has a similar viscosity to water, lipiodol is highly viscous and makes injection of the mixture difficult down a narrow-bore needle.²⁴ Glubran 2 and ocrylate have longer polymerization times than enbucrilate and therefore do not require dilution with lipiodol.^{12,25} The fluid used to prime and flush the injection needle can influence polymerization time: because saline solution will trigger glue polymerization, distilled water

Abbreviation: CSEMS, covered self-expandable metal stent.

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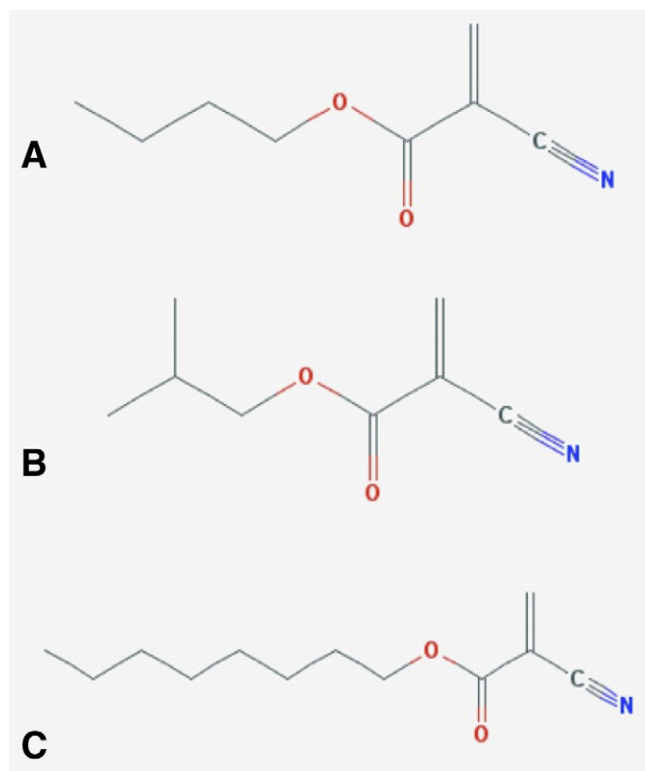


Figure 1. A, Structure of N-butyl 2-cyanoacrylate (enbucrilate). B, Structure of isobutyl 2-cyanoacrylate (bucrilate). C, Structure of 2-octyl cyanoacrylate (ocrylate) demonstrating differing alkyl chains.



Figure 2. Freehand glue injection of gastric fundal varices under endoscopic guidance with endoscope in retroflexion.

should be used for injection of enbucrilate. By contrast, the longer polymerization time of ocrylate allows the use of saline solution to prime and flush the needle.²⁵

Glue injection should be performed through a Luer lock injection needle catheter with a metal hub to avoid degradation by the glue. All staff should wear protective glasses to avoid accidental eye exposure to glue. The needle catheter should be primed with distilled water (or saline solution if ocrylate is used), and once intravariceal position of the needle is confirmed (by free flow of water into the varix without bleb formation), 1 mL of glue is injected followed by flushing with a volume of water equal to that of the needle catheter dead space (generally about 1 mL) to deliver the entire glue contents from the catheter into the varix. The needle is then removed from the varix and continuously flushed to keep the catheter patent for a possible second injection. Enbucrilate—even after dilution with lipiodol—needs to be injected rapidly over seconds to prevent premature solidification in the needle or gluing of the needle to the varix. By contrast, ocrylate can and should be injected more slowly over 45 to 60 seconds. Obliteration of the varix can be assessed by blunt palpation by using a closed forceps and additional glue injected in aliquots of 1 mL until the varix is hard to palpation.

To date, there are no randomized trials comparing undiluted ocrylate to enbucrilate diluted with lipiodol for the treatment of gastric varices. There are practical advantages to using ocrylate. Injection is easier because of the longer

allowable injection time and the consistency similar to that of water. The injection can be performed by using a standard sclerotherapy needle. The prolonged polymerization time also reduces the risk of damage to the endoscope. Prompt wiping will remove any ocrylate that accidentally comes into contact with the endoscope.

Endoscopic versus EUS-guided injection

Glue injection has been traditionally performed freehand under endoscopic guidance (Fig. 2). However, the injection is “blind” and may be paravariceal. Delivery of glue under EUS guidance through a standard FNA needle has the advantage of enabling real-time confirmation of delivery into the varix lumen. Furthermore, endoscopy may visualize only the “tip of the iceberg,” missing deeper varices. Boustière et al²⁶ showed that the use of EUS increases the detection of fundal varices 6-fold, and Lee et al²⁷ demonstrated that EUS monitoring of glue injection until obliteration reduced the risk of bleeding, with a possible reduction in mortality. Similarly, Iwase et al²⁸ showed residual patency of treated varices correlated with rebleeding risk after glue injection. Varix obliteration can be confirmed by the absence of blood flow on color Doppler.

EUS can display the main “perforator” feeding vein, which offers an additional target for glue therapy. In a small case series, Romero-Castro et al²⁹ injected the feeder vessel under EUS guidance by using a mixture of enbucrilate with lipiodol. Fluoroscopic visualization, enabled by lipiodol, confirmed accurate targeting of the feeder vessel. The authors speculated that targeting the perforating vessel rather than the varix lumen reduced the amount of glue needed to achieve obliteration of gastric varices and reduced the risk of embolization.

A practical advantage of EUS-guided treatment is the lack of dependency on direct varix visualization. Even in the presence of blood or retained food that may obstruct the endoscopic view, the varix lumen can be visualized and targeted for glue injection.

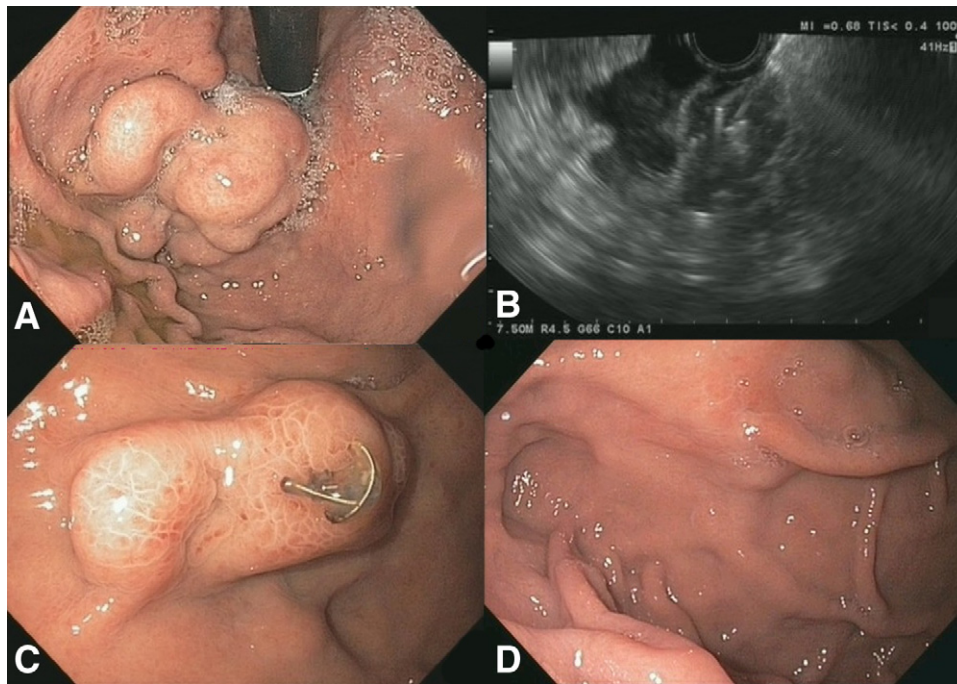


Figure 3. Obliteration of gastric fundal varices by using coils and ocrilate glue. **A**, Large, type 1 isolated gastric varices. **B**, EUS-guided injection of metal coil followed by injection of 1 mL ocrilate. **C**, Extravasation of metal coil from obliterated varix 6 weeks later. **D**, Varices eradicated at 1-year follow-up.

Glue embolization

A major, potentially life-threatening risk of glue injection of gastric varices is systemic embolization, primarily via highly prevalent splenorenal and gastorenal portosystemic shunts,²⁶ especially in type 1 isolated gastric varices.³⁰ Adverse events include pulmonary embolism, splenic vein and portal vein thrombosis (which can lead to hepatic decompensation in end-stage liver disease), splenic infarction, and recurrent sepsis because of embolized glue acting as a septic focus.^{31–41} Arterial embolization resulting in stroke and multiorgan infarction may occur with a patent foramen ovale or arteriovenous pulmonary shunts. Factors that may increase embolization risk include overdilution of enbucrilate with lipiodol, excessively rapid injection, injection of too large a volume of glue in a single injection, and type 1 isolated gastric varices that have high blood flow rates and can sweep away the glue before it has hardened. Other adverse events include visceral fistulization,⁴² which may occur after paravariceal injection.¹³

Combined coil and glue treatment

Stainless steel coils that are currently used for intravascular embolization treatments can be delivered under EUS-guidance and offer a new treatment approach (Fig. 3). A small case series described the deployment of commercially available coils into large gastric varices or the feeding perforating vein to achieve obliteration.⁴³ In a subsequent multicenter study, coil treatment alone required fewer endoscopies and had a lower risk of

severe adverse events such as embolization as compared with cyanoacrylate injection alone.⁴⁴

The intravariceal deployment of a coil before glue injection may minimize the risk of glue embolization. Ex-vivo work has shown that glue immediately adheres to the fibers of a “wool coil” when immersed in a container of heparinized blood.⁴⁵ The coil may therefore act as a scaffold to trap the glue within the varix at the site of injection. The coil itself also may contribute to varix obliteration and hemostasis, thereby decreasing the amount of glue needed to achieve variceal obliteration. The coil diameter after deployment (up to 20 mm) is selected to approximate that of the lumen of the targeted varix. In a cohort of 30 patients, combined coil and glue therapy was found to be safe and effective in eradicating gastric fundal varices, with only a single treatment session required in 96% of patients.⁴⁵ Immediate hemostasis was achieved in all patients with active bleeding. Rebleeding from incompletely treated gastric varices occurred in 1 patient; apart from this, there were no adverse events. The technique of combined coil and glue injection for gastric varices is outlined in Table 1. The technique can be applied for large varices anywhere in the GI tract and was recently reported for successful obliteration of large bleeding rectal varices.⁴⁶ Further studies are needed to assess whether EUS-guided glue injection with or without the use of coils is better than the conventional freehand approach in terms of safety and efficacy.

TABLE 1. Technique of combined coil and glue injection of gastric varices

1	The gastric fundus is filled with water to aid visualization of the varices.
2	A coil size is selected based on the diameter of the varix to be treated.
3	The varix is punctured with a saline solution-primed 19G or 22G FNA needle (depending on the size of coil to be delivered). Intravariceal position can be confirmed by either blood aspiration or by injection of saline solution that will produce a flow of bubbles.
4	The coil is loaded into the needle and advanced by using the stylet or the stiff end of a guidewire.
5	Coil deployment within the varix is monitored on US, visualized as a curvilinear echogenicity.
6	Coil deployment is immediately followed by 1 mL of undiluted ocrilate glue slowly injected over 45-60 seconds. The glue produces intense echogenicity and shadowing as it fills the varix lumen.
7	The needle is flushed with 1 mL saline solution to clear glue in the “dead space” then withdrawn into the sheath. The FNA needle is removed.
8	Several minutes are allowed for complete glue polymerization. Varix obliteration is confirmed with color Doppler flow.
9	Alternatively, the treated varix can be blunt “palpated” with a closed forceps under endoscopic guidance. An obliterated varix will be hard on palpation.

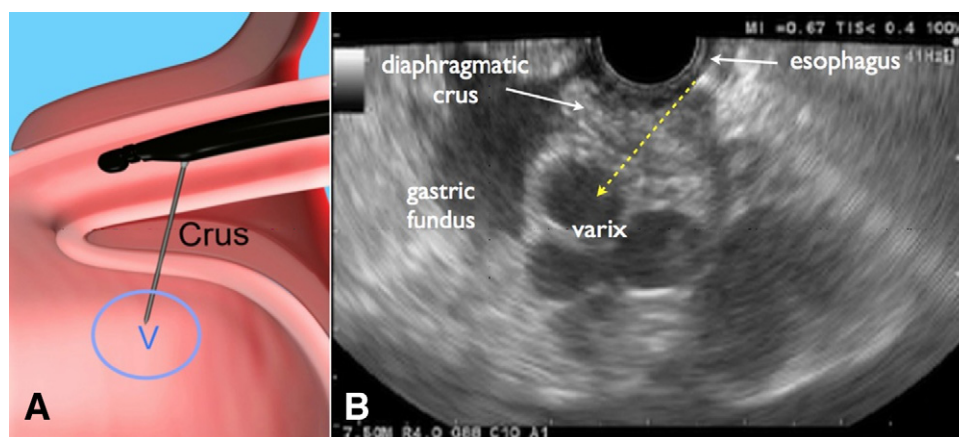


Figure 4. Transcural approach to gastric fundal varices. **A**, Anatomic diagram. **B**, EUS view. The yellow dashed line is the direction of the injection needle. V, fundal varix.

Transesophageal access to fundal varices

By using an echoendoscope, the gastric fundus can be imaged with the transducer positioned in the distal esophagus. Gastric fundal varices can be targeted by using a transesophageal approach by standard FNA technique⁴⁵ (Fig. 4). Transesophageal access to gastric varices enables injection with the echoendoscope in a straight position, unencumbered by gastric contents. By avoiding puncture across the gastric mucosa—often thinned out by large varices—“back-bleeding” into the gastric lumen after needle removal can be prevented. The interposed mural tissue includes the diaphragmatic crus muscle (left bundle of the right crus), seen as a hypoechoic band-like structure sandwiched between the walls of the esophagus and gastric fundus on US. This musculofibrous bundle acts as a stabilizing “backboard” to the fundal varices. In addition to preventing back bleeding, the bundle can prevent spillage of glue from the injected varix into the bowel lumen. This

is important because liquid glue can cause significant endoscope damage. Another advantage of the transesophageal approach is more direct access to the feeder vein.

ESOPHAGEAL VARICES

Enbucrilate injection of esophageal varices was first reported by Gotlib and Zimmermann⁴⁷ in 1984 and has since been used in the acute treatment of bleeding esophageal varices in a few series,⁴⁸ including randomized trials against band ligation for acute bleeding⁴⁹ and for eradication of high risk varices.⁵⁰ Overall, control of bleeding by using enbucrilate was found to be similar to band ligation, but rebleeding rates were higher. In addition, glue injection was found to be associated with sinus and fistula formation,^{42,51} in one case resulting in catastrophic bleeding.⁵² The higher complication rate may be explained by an increased risk of extravascular injection and attendant

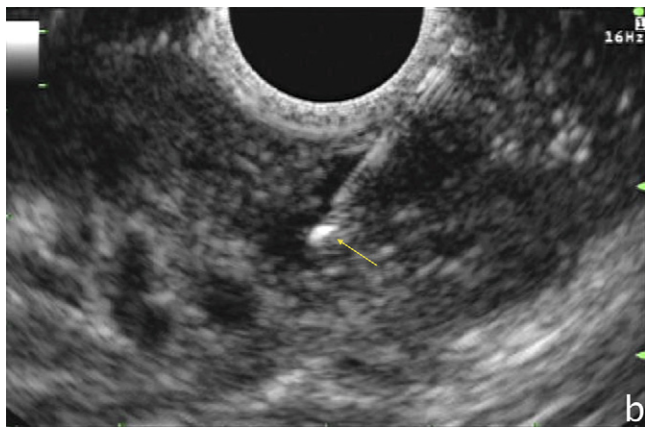


Figure 5. EUS-guided injection of a bleeding esophageal varix in a patient who failed prior band ligation therapy.

histotoxic reactions, owing to smaller lumen diameter. Our preference is to inject glue under EUS guidance so that needle position and intravascular glue delivery can be confirmed (Fig. 5). In view of the widespread use and excellent results of conventional band ligation for esophageal varices,^{53,54} glue treatment should be restricted to varices that are not candidates for or are refractory to band ligation (Fig. 6). Very large esophageal varices may be a contraindication to band ligation because of the risk of exsanguination from an incompletely ligated varix.⁵⁵

NON-VARICEAL HEMOSTASIS

Non-variceal upper GI hemorrhage is a common problem, with an incidence of 20 to 60 per 100,000 in European and Northern American populations,⁵⁶ although most cases have ceased bleeding by the time of endoscopy. Endoscopic management of active bleeding varies according to the site of bleeding and briskness but typically involves one or more of epinephrine or hypertonic saline solution injection, monopolar or bipolar diathermy, and the use of hemostatic clips or bands.⁵⁷

There is only one randomized trial regarding the use of glue in the management of non-variceal hemorrhage. Enbucrilate injection was compared with injection of hypertonic saline solution and epinephrine in the treatment of non-variceal bleeding in 118 patients with active bleeding or non-bleeding visible vessels at endoscopy.⁵⁸ Overall, initial hemostasis was similar in both groups, with a reduction in rebleeding with glue treatment only in those with active arterial bleeding at endoscopy. There were, however, two cases of glue embolization with infarction, one fatal. In a retrospective, 3-year review from a single, tertiary-care unit in Italy, 18 patients with failure of hemostasis or early rebleeding from a non-variceal upper GI source were treated with intralesional injection of adrenaline and enbucrilate, with successful hemostasis in 17.⁵⁹ There were no reports of immediate or delayed adverse events.

Levy et al⁶⁰ reported the successful use of cyanoacrylate injection under EUS guidance to embolize the feeding artery of a bleeding duodenal artery refractory to heater probe and epinephrine injection, and two cases of bleeding from GI stromal cell tumors by direct injection of 3 to 5 mL glue into the center of the tumor. It was noted in the one GI stromal cell tumor case with endoscopic follow-up that the glue had caused extensive tumor necrosis by the following day.

Two case series of 4 and 5 patients, respectively, have described the successful use of topically sprayed enbucrilate to achieve hemostasis in bleeding GI tumors, an endoscopic mucosal resection site, and duodenal ulcer that were not controlled with epinephrine injection^{61,62} (Fig. 7). This technique is straightforward to perform, and, by not injecting into tissue or blood vessels, avoids the risks of embolization and tissue necrosis. Although the technique is effective at achieving initial hemostasis by a tamponade effect, rebleeding may occur when the glue “escar” detaches from the surface. Additionally, it should be noted that there is the possibility of total occlusion of a narrow lumen if excessive quantities of glue are injected, so caution is advised when using this technique in a lumen such as the esophagus.

There are several reports of adverse events of using glue to treat non-variceal hemorrhage by direct injection, including pancreaticoduodenal necrosis, duodenal ulcer perforation, and esophageal sinus formation.⁶³⁻⁶⁵

BILIARY LEAKAGE

A significant bile leak complicates 0.5% to 1.1% of laparoscopic cholecystectomies, usually from the cystic duct stump, and sometimes from a duct of Luschka, cystohepatic duct, or major extrahepatic or intrahepatic ducts.^{66,67} Bile leaks also may complicate other hepatobiliary surgeries or trauma. Standard endoscopic management involves placement of a large-bore (eg, 10F) plastic stent or nasobiliary drain, plus or minus a biliary sphincterotomy.^{67,68} The goal is to reduce distal biliary pressure so that bile preferentially drains into the duodenum rather than through the defect, allowing the defect to heal. Up to 10% of leaks, however, may not respond to such initial endoscopic therapy,⁶⁹ particularly if the leak involves a major duct.⁷⁰ For persistent leaks despite plastic stenting, a covered self-expandable metal stent (CSEMS) may be used,⁷¹⁻⁷³ although this may be compromised by stent migration and in some circumstances by biliary strictures.^{73,74} CSEMSs also entail significant cost, with a list price in the order of \$1600.⁷⁵

An alternative approach is to occlude the leaking duct with glue injection, first reported in 2002.⁷⁶ Table 2 summarizes the published experience of this method and includes our unpublished data. All cystic duct leaks were sealed in the first ERCP session with no adverse

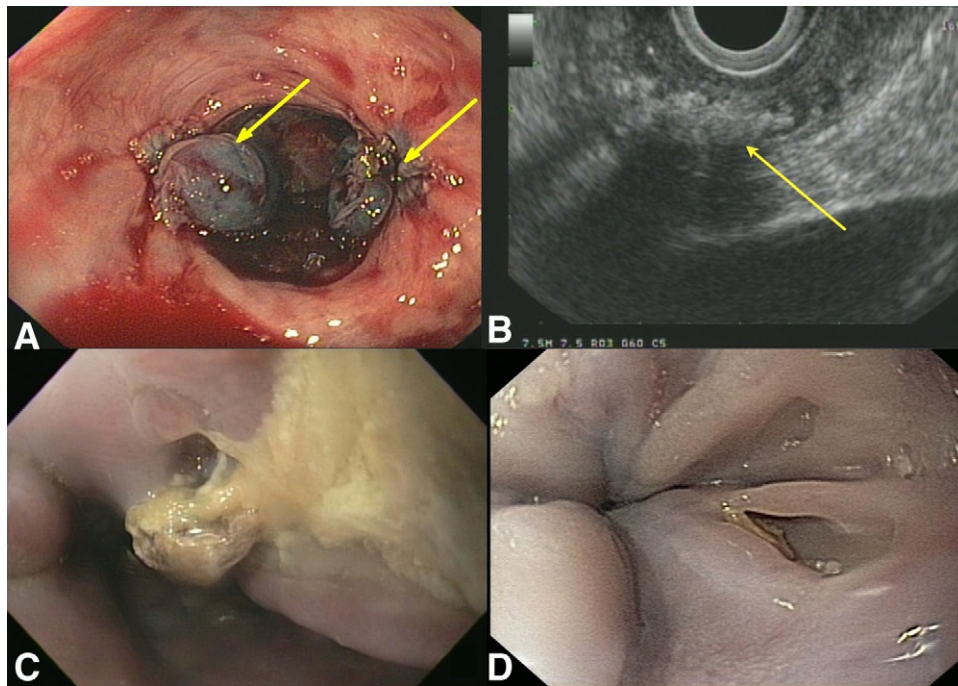


Figure 6. Treatment of esophageal varices with cyanoacrylate. **A**, Recurrent bleeding despite prior band ligation treatment (*arrows*). **B**, Intraluminal cyanoacrylate (*arrow*) after injection under EUS guidance. **C**, Extrusion of glue after 9 days. **D**, Scarred cavity from obliterated varix remains after 3 months.

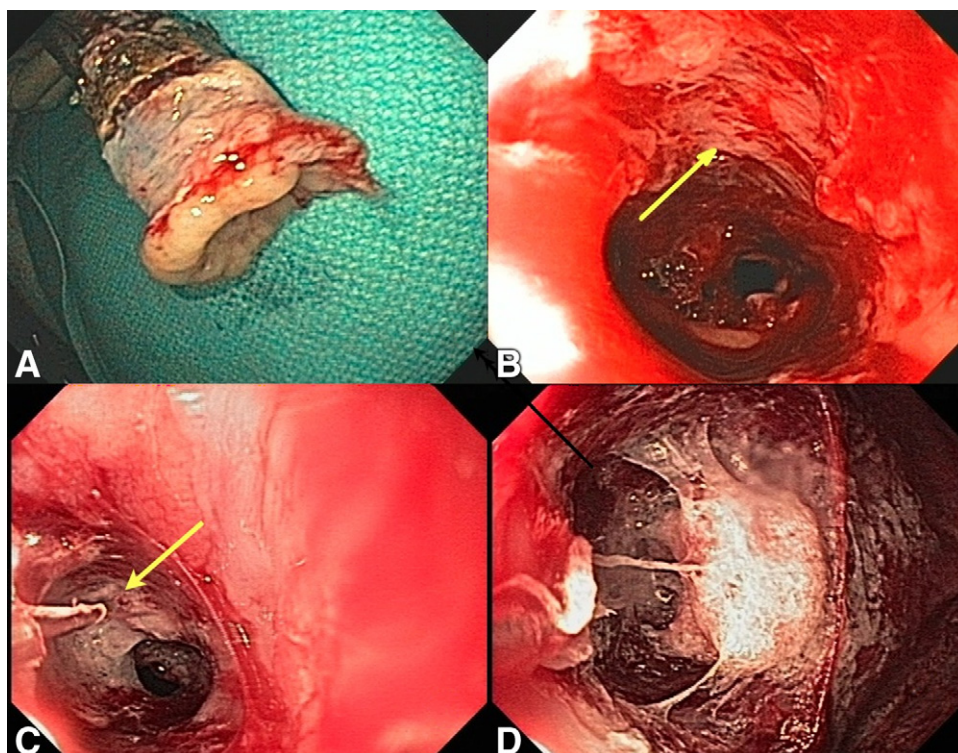


Figure 7. Use of cyanoacrylate spray for hemostasis. **A**, Tissue ingrowth and overgrowth into a partly covered esophageal stent results in partial mucosectomy on stent removal. **B**, Extensive bleeding from mucosectomy site. **C**, Cyanoacrylate is sprayed directly onto the bleeding mucosa (*needle tip arrowed*). **D**, Complete hemostasis achieved.

TABLE 2. Published series and our unpublished data on sealing of biliary leaks with cyanoacrylate

Sex/age, y	Cause of leakage	Leak site	Prior therapy	Glue mixture	Glue volume	Treatments (no.)	Outcome	Follow-up	Ref
M/82	Laparoscopic cholecystectomy	Cystic duct	ES, NBD	En/Lip 0.5:0.3	1 mL	1	Completely sealed	Cholangiogram normal at 1 wk	76
M/58	Laparoscopic cholecystectomy	Cystic duct	ES, 10F stent	En/Lip 0.5:0.3	0.8 mL	1	Completely sealed	Asymptomatic after 51 mo	76
M/52	Pancreatic tail resection, cholecystectomy, portal vein reconstruction	Common bile duct	ES, 10F stent	En/Lip 0.5:0.3	0.8 mL	1	Completely sealed	Normal cholangiogram after 4 mo	76
M/47	Liver gunshot injury	Right hepatic lobe	ES	En/Lip 0.5:0.3	0.8 mL	1	Completely sealed	Laparotomy 2 mo later showed hepatic necrosis, no biliary leak	76
F/51	Liver gunshot injury	Right hepatic lobe	ES, NBD	En/Lip 0.5:0.3	1.5 mL	1	Completely sealed	Asymptomatic after 160 mo	76
F/50	Traumatic liver rupture	Right hepatic duct	ES, 10F stent	En/Lip 0.5:0.3	0.8 mL	1	Completely sealed	Normal cholangiogram at 16 mo	76
F/48	Left hemihepatectomy for hemangioma	Resection margin	ES, 10F stent	En/Lip 0.5:0.3	0.8 mL	1	Completely sealed	Normal cholangiogram at 103 mo	76
F/62	Right hemihepatectomy for colon cancer metastasis	Resection margin	ES, 10F stent	En/Lip 0.5:0.3	1 mL, 1 mL	2	Temporarily sealed	Enterophrenico-hepaticostomy	76
M/15	Left hemihepatectomy for hepatoma	Resection margin	ES, 7F stent	En/Lip 0.5:0.3	0.9 mL	1	Failed to occlude fistula	Hepaticojejunostomy	76
M/51	Laparoscopic cholecystectomy	Cystic duct		En, coils		1	Completely sealed		77
F/37	Open partial cholecystectomy	Cystic duct	ES, 10F, 7F stents	En/Lip 1:1	1 mL	1	Completely sealed	Cholangiogram normal at 6 mo	78
M/51	Right hemihepatectomy for colon cancer metastasis	Resection margin	ES, 10F stent	En	0.5 mL, 1 mL	4	Completely sealed	Cholangiogram normal at 3 mo	*
F/54	Right hepatectomy for hepatoma	Resection margin	ES, 10F stent	En	1 mL	1	Completely sealed	Cholangiogram normal at 3 wk	*
M/64	Laparoscopic cholecystectomy	Cystic duct	ES, 10F stent, 8-mm × 8-cm covered SEMS	En	0.5 mL	1	Completely sealed	Cholangiogram normal at 10 wk	*
M/84	Laparoscopic cholecystectomy	Cystic duct	ES, 10F stent	En	1 mL	1	Temporarily sealed	Repeat cholangiogram after 4 wk showed smaller leak, completely sealed with 2 × 10F stents at 3 mo	*

Ref, reference; M, male; ES, endoscopic sphincterotomy; NBD, nasobiliary drain; En, enbucrilate; Lip, lipiodol; F, female; SEMS, self-expandable metal stent.

*Our unpublished data.

events. Of the patients with liver injury or post-hepatectomy leaks, 75% had complete sealing with from 1 to 4 treatments, and none of the patients had glue injection-related adverse events.

Our technique involves placement of a guidewire into the cystic duct stump and/or leaking segment and a second guidewire into the common hepatic and/or main segmental duct, over which a plastic stent is

placed (Fig. 8). This prevents back leakage of glue obstructing the main bile duct. A cannula is passed into the cystic duct and/or leaking segment over the guidewire, which is then withdrawn, and 0.5 to 1 mL of undiluted enbucrilate is injected into the cystic duct stump over 10 to 15 seconds, followed by a flush of distilled water equivalent to the dead space of the cannula.

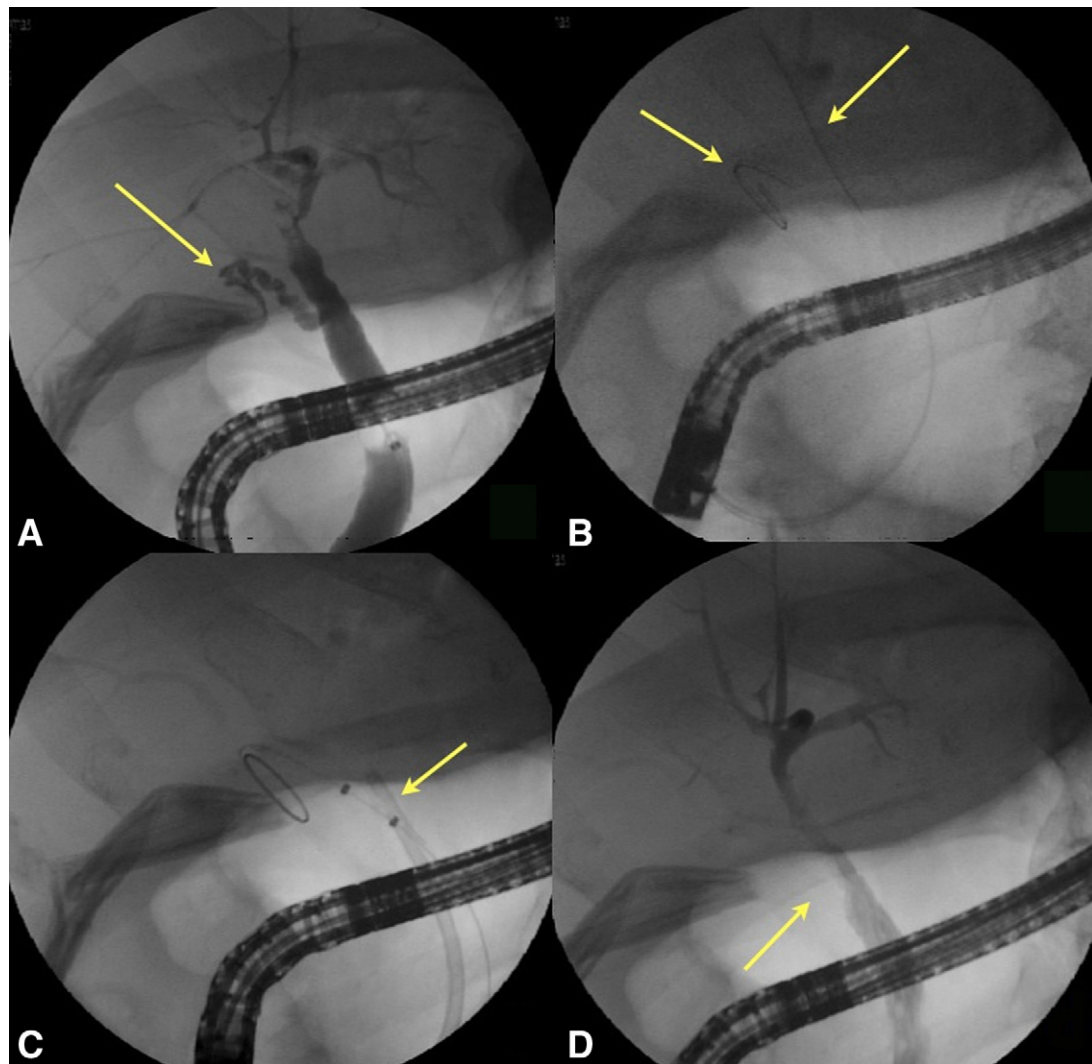


Figure 8. Sealing cystic duct leak with enbucrilate. **A**, Bile leak from cystic duct (*arrow*). **B**, Guidewires inserted into cystic duct (*left arrow*) and common hepatic duct (*right arrow*). **C**, Common hepatic duct is stented with 10F × 9-cm polyethylene stent (*arrow*), cannula passed over guidewire into cystic duct, and 0.5-mL undilute enbucrilate is injected. **D**, Post-injection cholangiogram shows that leak has sealed.

PANCREATIC FISTULA

A pancreatic fistula is a potential complication of acute necrotizing pancreatitis, chronic pancreatitis, pancreatic surgery, and trauma.⁷⁹ The fistula leak may become encapsulated as a pseudocyst or it may communicate internally with the pleural or peritoneal cavities or externally with the skin, generally through tracts created by surgical or radiologic procedures.^{80,81} Patients with severe pancreatitis associated with fistulas are significantly more likely have a prolonged inpatient stay.⁸²

Management involves medical stabilization, optimizing nutrition, and percutaneous drainage of collections. If conservative treatment fails, most cases are manageable endoscopically by placement of a pancreatic stent or naso-pancreatic catheter.⁸¹ Stents or drains can become occluded or dislocated, compromising success, and in complex cases they may not work at all. Direct sealing of

the pancreatic duct leak by using fibrin glue was first reported in 1990,⁸³ but because of the glue's degradation by pancreatic enzymes, multiple applications are usually required.⁸⁴

Several, mostly small, case series have demonstrated the efficacy of enbucrilate injection in sealing refractory pancreatic fistulas, with success rates of 67% to 100% (Table 3). Cyanoacrylate glue appears to be superior to fibrin glue in that sealing of the fistula usually can be achieved in a single procedure.⁸⁴ The volume of glue used was dependent on the size of the fistula and varied from 0.5 mL to 3 mL in the case series. The major risk of the technique is accidental injection of glue into the main pancreatic duct or displacement of the glue out of the fistula such that the fistula fails to heal. Careful location of the fistula is imperative, and glue displacement can be reduced by very slow injection of the final 1 mL of sterile water used to flush glue out of the injection catheter.

TABLE 3. Published case series using cyanoacrylate glue to seal pancreatic fistulas

Reference	No. patients	Fistula sealed (%)	Glue mixture
Seewald et al 2004 ⁸⁴	12	67	Enbucrilate/lipiodol
Mutignani et al 2004 ⁸⁵	4	75	Glubran/lipiodol
Romano et al 2008 ⁸⁶	1	100	Glubran/lipiodol
Labori et al 2009 ⁸¹	4	100	Enbucrilate/lipiodol

GASTROINTESTINAL FISTULA

Cyanoacrylate glue has been used to seal fistulae outside of the GI tract for 40 years.⁸⁷ In the GI tract, the use of glue was first reported in the treatment of a tracheoesophageal fistula in 1983.⁸⁸ Since then, there have been many reports of successful fistula closures by using glue either as a single agent or in combination with other modalities such as stenting.⁸⁹⁻⁹⁴ There are, however, no controlled trials.

Three case reports describe the use of enbucrilate injection as an emergency measure to halt bleeding from an aortoenteric fistula, allowing the patient to be stabilized for placement of an endovascular graft as definitive therapy.⁹⁵⁻⁹⁷ A similar case report describes success in treating a bleeding azygos-esophageal fistula.⁹⁸ Cyanoacrylate glue appears ideally suited for hemostasis of bleeding complicating bleeding.

A recent prospective case series from France⁹⁹ reported the use of glue in 15 patients to close small (<1 cm) fistulae after bariatric surgery although long-term fistula closure rates were not provided. Given the inert constitution and histotoxicity of glue, we have concerns about the durability of fistula closure, particularly if the glue fills the entire tract and is later expelled. One study following 22 patients with endoscopic sealing of tracheoesophageal fistulae by using fibrin or enbucrilate glues found that 45% had recurrent fistulae at a median of 46 days after initial closure.¹⁰⁰ In a series of 10 patients treated with enbucrilate for fistulae complicating Crohn's disease, malignancy, and surgery, only 3 patients achieved healing, with a median of two treatments.¹⁰¹

The method of glue delivery to close a fistula deserves further study. It may be preferable to seal only the fistula opening (mouth) and avoid instillation of the glue into the fistula tract so that this can close by granulation. Direct injection of glue into tissue should be avoided because this risks histotoxicity that can cause sinus or fistula formation.

SUMMARY

There are now more than 25 years of experience with the endoscopic use of cyanoacrylate glues in the GI tract. In patients with bleeding or large fundal gastric varices, glue treatment is widely considered the standard of care, with high hemostasis rates during acute bleeding and efficacy in bleeding prevention and variceal obliteration as secondary and primary prophylaxis. Embolization is a rare, but potentially lethal, complication. The combination of EUS-guided coil placement before glue injection may reduce the embolization risk. Ocrylate appears to be at least equivalent to enbucrilate in terms of safety and is easier to administer under EUS guidance because of a longer polymerization time.

In acute esophageal variceal bleeding, glue treatment may be useful for very large varices or varices refractory to conventional band ligation. EUS guidance deserves further study to avoid extravascular injection into the esophageal wall.

Cyanoacrylate injection appears well-suited as a means of sealing leaks refractory to standard endoscopic treatment by sphincterotomy and plastic stenting in the biliary tree and the main pancreatic duct. In a majority of cases, leak closure is accomplished after a single treatment. Because of its significantly lower cost, glue injection may be preferable to the use of CSEMSs as the next step for refractory biliary leaks, particularly for intrahepatic leaks.

Significant numbers of case reports and some series suggest that cyanoacrylate glue may have a role in the sealing of GI fistulas in patients not suitable for surgery. Because of the lack of any controlled trials, true efficacy rates are not available, but data would suggest that glue is poorly effective in healing inflammatory or malignant disease-related fistulas.

Dedication

This review is dedicated to the "father" of endoscopic glue therapy, Nib Soehendra, MD, on the occasion of his 70th birthday.

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