Communication from the ASGE Technology Committee

TECHNOLOGY STATUS EVALUATION REPORT

Tissue adhesives: cyanoacrylate glue and fibrin sealant

The ASGE Technology Committee provides reviews of existing, new, or emerging endoscopic technologies that have an impact on the practice of GI endoscopy. Evidence-based methodology is used, performing a MEDLINE literature search to identify pertinent clinical studies on the topic and a MAUDE (U.S. Food and Drug Administration Center for Devices and Radiological Health) database search to identify the reported adverse events of a given technology. Both are supplemented by accessing the "related articles" feature of PubMed and by scrutinizing pertinent references cited by the identified studies. Controlled clinical trials are emphasized, but in many cases, data from randomized, controlled trials are lacking. In such cases, large case series, preliminary clinical studies, and expert opinions are used. Technical data are gathered from traditional and Web-based publications, proprietary publications, and informal communications with pertinent vendors. Technology Status Evaluation Reports are drafted by 1 or 2 members of the ASGE Technology Committee, reviewed and edited by the Committee as a whole, and approved by the Governing Board of the ASGE. When financial guidance is indicated, the most recent coding data and list prices at the time of publication are provided.

For this review, the MEDLINE database was searched through August 2012 for relevant articles by using the key words cyanoacrylate, cyanoacrylate glue, cyanoacrylate and gastroenterology, cyanoacrylate and endoscopy, fibrin glue, fibrin sealant, tissue glue and endoscopy. Technology Status Evaluation Reports are scientific reviews provided solely for educational and informational purposes. Technology Status Evaluation Reports are not rules and should not be construed as establishing a legal standard of care or as encouraging, advocating, requiring, or discouraging any particular treatment or payment for such treatment.

BACKGROUND

Tissue adhesives are compounds that can be used for hemostasis, wound closure, or fistula repair. The main classes of tissue adhesives are cyanoacrylate glues, fibrin glue, and thrombin. Cyanoacrylate glues are used primarily for endoscopic control of bleeding from gastric varices and less commonly for hemostasis of other bleeding lesions. They are also used for closure of fistulae and anastomotic leaks. Fibrin glue (fibrinogen and thrombin) and thrombin have also been used endoscopically for the treatment of bleeding. This status evaluation report reviews the described uses of cyanoacrylate glues, fibrin glue, and thrombin in endoscopy.

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TECHNOLOGY UNDER REVIEW

Cyanoacrylates

Cyanoacrylates are a class of synthetic glues that rapidly solidify on contact with weak bases, such as water and blood.[1] Several manufacturers produce cyanoacrylate glues (Table 1). Some are available in the United States and are approved by the U.S. Food and Drug Administration for medical use (eg, wound closure). They are used off-label in the United States for endoscopic applications.

METHOD

Cyanoacrylate glue is a liquid that may be mixed with lipiodol, an oily contrast agent, before injection. Mixing cyanoacrylate glues with lipiodol slows the rate of solidification, thereby facilitating endoscopic administration via needle injection and reducing the risk of inadvertent adherence to catheters and endoscopes. It also allows visualization of the injected varix on fluoroscopy. Various ratios of glue and lipiodol are used, ranging from 1:1 to 1:1.6.[1] Overdilution may increase the risk of embolization before the glue can solidify at the time of injection. Some cyanoacrylates (eg, Dermabond, Ethicon, Somerville, NJ; Glubran, Aspide Medical, La Talaudière, France) polymerize more slowly and thus do not require the use of lipiodol for injection.

The exact approach to glue injection for gastric varices is not standardized, although 1 retrospective study demonstrated good efficacy and safety with a standardized regimen.[2] In general, the following steps are taken. Before injection of the glue, silicone oil or other similar compounds can be used to coat the tip of the endoscope to minimize the risk of glue adherence and damage to the instrument. Additionally, lipiodol alone may be injected into the working channel of the endoscope to coat it and prevent glue adherence. A large-bore sclerotherapy needle (21-22 gauge) may be primed with either lipiodol or normal saline solution. The vessel targeted for treatment is then punctured, and 1 mL is injected (which

TABLE 1. List of different commercially available cyanoacrylate preparations available for medical use

Trade name	Manufacturer	Active component	Sold as	Polymerization rate	Require lipiodol	Cost/ ampoule (U.S.$)	Available in the U.S.
Indermil	Covidien	*N*-butyl-2-cyanoacrylate	0.5-mL liquid/ampoule	Faster	Yes	26	Yes
Histoacryl	TissueSeal	*N*-butyl-2-cyanoacrylate	0.5-mL liquid/ampoule	Faster	Yes	27	Yes
Dermabond	Ethicon	2-Octyl-cyanoacrylate	0.5-mL liquid/ampoule	Slower	No	25	Yes
Glubran 2	GEM, Italy	*N*-butyl-2-cyanoacrylate + methacryloxysulfolane	0.25-, 0.5-, and 1-mL liquid/ ampoule	Slow	No	—	No

will consist of the primer used). This should flow without resistance, indicating an intravascular puncture. The glue is then injected rapidly, followed by distilled water or saline solution to flush out the channel while the needle is still in the varix. Because the cyanoacrylate/lipiodol mixture is very viscous, a 2-mL syringe with a Luer lock (Becton, Dickinson and Company, Franklin Lakes, NJ) is recommended to allow rapid injection and to prevent spraying.[3] Expert opinion suggests that individual injections of glue are limited to volumes of 0.5 to 1.0 mL to minimize the risk of embolization,[1] although data to support the optimal volume are lacking and may need to be tailored to the size of the varix.

When injected intravascularly, cyanoacrylate glue solidifies, producing a cast of the vessel. Subtotal occlusion is immediate, and total occlusion occurs within hours.[4,5] After injection into a gastric varix, the overlying mucosa sloughs off and the cast of glue begins extruding into the gastric lumen after about a month with complete extrusion by 3 months.[1,6] Repeat endoscopy is generally performed to assess the response to therapy. Data regarding the optimal method for surveillance and time intervals at which it should be performed are lacking.

Fibrin sealant

Fibrin sealant contains 2 components: highly purified, freeze-dried human fibrinogen with factor XIII and a starter solution containing human thrombin. The component solutions are reconstituted in 2 separate syringes with sterile water immediately before use. When mixed, these agents form a clot by mimicking the terminal phase of the physiologic clotting cascade, initially producing fibrin monomers that subsequently assemble into a stronger cross-linked fibrin polymer. Thrombin also activates factor XIII, which facilitates the bonding of the fibrin polymer (Fig. 1).[7] Fibrin glue is fully absorbed by macrophages and fibroblasts within 2 weeks of application.[8]

Fibrin glue is available commercially in the United States from several sources. Tisseel (Baxter, Westlake Village, Calif), Evicel (Johnson & Johnson, Somerville, NJ), and Hemaseel (Hemacure, Sarasota, Fla) are approved for topical application, hemostasis, and sealing of anastomoses in various surgical disciplines. Although fibrin glues have been used in Europe for endoscopic hemostasis in bleeding ulcers and varices, product labeling in the United States does not endorse intravascular injection.

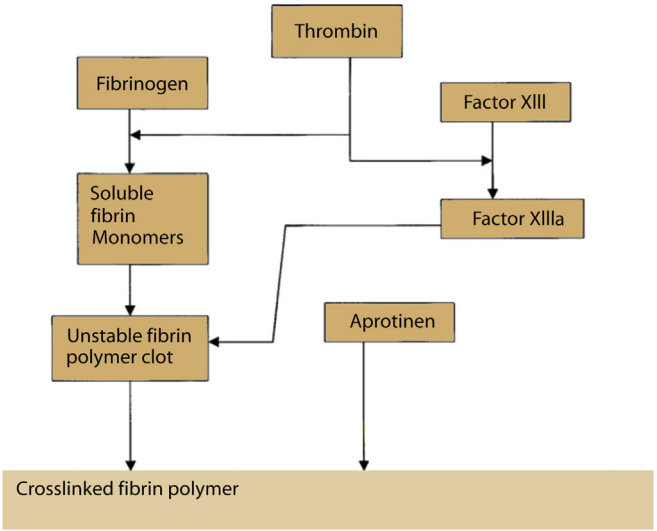

Figure 1. Schema of fibrinogen and thrombin interaction to yield a mature fibrin glue clot. Adapted from Dunn et al.[7]

When used during endoscopy, fibrin sealants may be delivered through specialized double-lumen catheters that are available with the product; these are passed through the endoscope. Because of the rapidity of clot formation, injection of the 2 major components (fibrinogen and thrombin) usually is performed either sequentially or by using a double-plunger syringe, which allows mixing while the agents are injected.

Thrombin

Thrombin promotes the conversion of fibrinogen to fibrin, producing a local fibrin clot. Human-derived thrombin is available commercially and from local blood bank sources and has largely supplanted bovine thrombin. It is a liquid preparation delivered topically to a bleeding lesion

through a catheter by a method similar to the use of fibrin sealant.

A newer thrombin-containing compound, Floseal (Baxter), has been used for hemostasis in a few case reports.[9-11] It consists of a bovine-derived matrix of gelatin granules that is mixed with a human-derived thrombin component to produce a gel-like complex. This can effect hemostasis in excavated lesions.

EFFICACY AND COMPARISON WITH AVAILABLE TECHNOLOGIES

Cyanoacrylates for bleeding

Gastric varices. Gastric variceal bleeding is a difficult clinical problem because band ligation and sclerotherapy are much less effective in this location compared with therapy for esophageal varices.[12,13] Placement of a transcutaneous intrahepatic portosystemic shunt (TIPS) has been the first line therapy in the United States. However, many patients are not good candidates for TIPS or other radiologic interventions, and this therapy is not available in all facilities. Cyanoacrylate glues have been used commonly in the treatment of gastric varices outside the United States.

One randomized, controlled trial (RCT) of 37 patients comparing cyanoacrylate injection with sclerotherapy with alcohol for bleeding fundal varices found that initial hemostasis rates were similar (89% vs 62%, P = not significant), but glue was more effective in obliterating varices (100% vs 44%, $P < .05$).[14] A nonrandomized study comparing cyanoacrylate with ethanolamine sclerotherapy found that glue was superior for initial hemostasis (93% vs 67%, $P = .014$).[15] Cyanoacrylate injection was compared with band ligation for bleeding gastric varices in an RCT; this study of 60 patients found that cyanoacrylate had a higher initial hemostatic rate (87% vs 45%, $P = .03$) and a lower rate of rebleeding (31% vs 54%, $P = .005$).[16] Two retrospective studies compared cyanoacrylate injection with TIPS for bleeding gastric varices. One found no difference in rebleeding rates at 72 hours, 3 months, and 1 year, and no difference in 3-month survival.[17] The other found that cyanoacrylate therapy had a higher 30-day rebleed rate than TIPS, although notably the rebleed rate in this study was higher than that reported previously in the literature. As secondary prophylaxis, cyanoacrylate glue injection has been shown to reduce rebleeding rates compared with band ligation[18] and propranolol.[19] As primary prophylaxis, cyanoacrylate glue therapy has been shown to reduce the risk of bleeding and mortality from varices more than 10 mm diameter compared with propranolol alone.[20]

Taken together, these data suggest that endoscopic therapy with tissue glue achieves initial hemostasis of bleeding gastric varices in 80% to 90%, is more effective than band ligation or sclerotherapy for primary control of gastric variceal hemorrhage, and is probably equivalent to TIPS. Glue therapy is likely superior to band ligation and β-blocker therapy for secondary prophylaxis against rebleeding.

Cyanoacrylate injection has been traditionally performed under endoscopic guidance only. A case series described the use of EUS to guide injection and monitor the results.[21] Another small series used EUS to identify and inject feeding "perforator" varices.[22] Another new technique described intravariceal deployment of a metal coil (similar to that used by interventional radiologists) before glue injection under direct EUS guidance. The coil is intended to act as a scaffold to retain the glue within the varix and decrease the risk of embolization. Hemostasis was achieved in 100% of 30 patients in the study, with complete obliteration of gastric varices in 96% patients after a single treatment, as seen on follow-up endoscopy. No procedure-related adverse event or evidence of glue embolization was seen in this patient cohort.[23] No comparison of EUS-guided glue injection with glue injection without EUS guidance is available.

Esophageal varices. Two randomized trials compared cyanoacrylate glue injection with band ligation for acute bleeding[24] and for primarily prophylaxis of high-risk esophageal varices.[25] Overall, control of bleeding by using cyanoacrylate glue appears similar to band ligation, but rebleeding rates are higher with glue injection. For primary prophylaxis, variceal eradication was similar, but adverse events and bleeding rates were higher in the glue arm. In addition, glue injection has been associated with esophageal sinus formation[26] and esophagovascular fistulae, potentially with catastrophic results.[27]

Nonvariceal hemostasis. Older case series described the use of cyanoacrylate glue in the treatment of bleeding peptic ulcers, but it has not been compared with the current standard treatments (epinephrine plus thermal therapy or clips). A case series describes the use of EUS to guide successful cyanoacrylate injection into a feeding vessel of a bleeding duodenal ulcer in 1 patient and into bleeding GI stromal tumors in 2 patients.[28] Two case series of 4 and 5 patients, respectively, described the successful use of topically sprayed cyanoacrylate glue to achieve hemostasis in bleeding GI tumors, an EMR site, and duodenal ulcer that were not controlled with epinephrine injection.[29,30]

Fibrin glue/thrombin for bleeding

Fibrin glue and thrombin have not been adequately evaluated in the treatment of bleeding peptic ulcers or varices compared with standard therapy used today. Several older trials compared injection of fibrin glue or thrombin with other hemostatic modalities for the treatment of bleeding gastroduodenal ulcers.[31-40] None evaluated fibrin glue compared with currently standard multimodality treatment by using epinephrine injection plus contact thermal probes or endoclips.

Fibrin glue has been injected for arrest of variceal bleeding in small uncontrolled series.[41,42] Thrombin also has

been evaluated for use in endoscopic hemostasis of variceal bleeding. Thrombin plus ethanolamine was equivalent to ethanolamine alone in 1 RCT.[43] In 2 retrospective studies, thrombin reportedly achieved hemostasis in bleeding gastric varices in 75% to 94%.[44,45] However, product labeling states that intravascular injection of fibrin glue is contraindicated because of the risk of embolization.

Cyanoacrylates for fistulae

Case series have described the successful use of cyanoacrylate glues for the endoscopic treatment of refractory bile leaks,[46] pancreatic fistulae[47-50] and a variety of other GI tract fistulae[51-56]; however, there are no controlled trials.

Fibrin glue for fistulae

An RCT of 13 patients with persistent enterocutaneous fistulae found that fibrin glue achieved closure after a mean of 2 days compared with 13 days with conservative therapy ($P < .01$).[57] An RCT compared fibrin glue with fistulotomy for anal fistulae; no advantage was found for simple fistulae, but the glue healed more complex fistulae.[58] Other series found lower success rates and high short-term recurrence rates, however.[59,60] A recent randomized trial comparing fibrin glue with observation only for Crohn's patients with anal fistulae found higher closure rates in the glue patients (38% vs 16%, $P = .04$).[61] Numerous case series report achieving prompt closure with the use of fibrin glue for enterocutaneous fistulae,[62-66] including persistent gastrocutaneous fistulae after gastrostomy tube removal.[67,68] Fibrin glue has been used to close esophageal perforations in case reports.[69,70] A single case report exists of successful closure of a duodenal perforation with fibrin glue.[71] These data are scant but suggest that fibrin glue is a reasonable option for persistent enterocutaneous fistulae.

SAFETY

The major risk of glue injection treatment of gastric varices is systemic embolization.[72] Reported embolic adverse events include pulmonary embolism, stroke, and multiorgan infarction via patent foramen ovale or arteriovenous pulmonary shunts, splenic infarction, splenic vein and portal vein thrombosis, and recurrent sepsis caused by embolized glue acting as a septic focus.[73-83] A retrospective radiologic study showed a 4.3% rate of pulmonary embolism after glue injection.[84] Use of undiluted glue resulted in no cases of embolization in 170 patients.[85] Transient pain and fever after cyanoacrylate glue injection are common and occur in as many as 90% of patients.[86,87] A recent large retrospective study of 751 patients who had undergone glue injection for gastric variceal bleeding found adverse events in 51 (6.8%), including 3.3% with rebleeding caused by early extrusion of the glue cast, 1.3% with sepsis, 0.7% with embolism, and death in 4 (0.53%).[88] Other adverse events include visceral fistulization, which may be a consequence of extravascular injection.[89] Instrument damage can result from glue contamination, including occlusion of the working channel and glue adherence to the tip of the endoscope. Adherence of the needle to the varix has also been reported.[1]

There are several reports of adverse events with the use of cyanoacrylate glue to treat nonvariceal hemorrhage by direct injection including duodenal ulcer perforation and esophageal sinus formation.[90,91]

Injection therapy with fibrin glue/thrombin is generally well tolerated. As with any blood product, potential adverse events include anaphylaxis, antibody formation against fibrinogen and thrombin leading to coagulopathy and bleeding, and infectious disease transmission.[92,93] Inadvertent intra-arterial injection of fibrin glue or thrombin may risk systemic embolization.[94]

Air embolization and death have occurred during fistula treatment with injection of both cyanoacrylate and fibrin glues. This has been attributed to overinsufflation within the fistula track.[95] When treating aerodigestive fistulae through the GI lumen, there is a risk of tracheobronchial accumulation and airway plugging from overflow of excessive volumes of glue.

EASE OF USE

Although most endoscopists are familiar with injection therapy in the GI tract, cyanoacrylates can be technically challenging to use because of the number and necessary rapidity of the process, and familiarity with the exact steps of the procedure planned is advisable before initiating treatment. Given the potential risks associated with the use of cyanoacrylate glue for gastric variceal treatment, preparation and arrangement of equipment and glue components before therapy are important for safe and efficient use. Extra personnel should be available to assist with the procedure. Staff and patients should use protective eyewear during preparation and injection. The cyanoacrylates should be refrigerated.

Fibrin glue is somewhat easier to use than cyanoacrylate glue. Premature clotting can occlude injection catheters, particularly single-channel varieties. There is no risk to the endoscope from contact with the fibrin clot.

FINANCIAL CONSIDERATIONS

Comparisons between TIPS and cyanoacrylate glue for bleeding caused by gastric varices have shown that glue is more cost-effective.[96,97] Damage to the endoscope with cyanoacrylate glue can sometimes be repaired but may require disposal and replacement of the entire instrument.

Pharmacy costs for the various cyanoacrylate and fibrin glue preparations are shown in Table 1. Endoscopic

applications of biologic or synthetic glues also may require use of a dual-plunger syringe and single- or dual-channel injection needles.

The CPT code used for esophagoscopy with injection sclerosis of varices is 43204. For EGD with injection of gastric or esophageal varices, the CPT is 43243.

AREAS FOR FUTURE RESEARCH

Evidence-based, standardized protocols for use of cyanoacrylate glue in gastric variceal bleeding need to be developed. Comparisons of different glue formulations should be performed. Randomized controlled trials should be conducted comparing TIPS to cyanoacrylate glues in patients who are candidates for TIPS. Further evaluation of methods to reduce the risk of systemic embolization from glue therapy is needed. Definition of the role of EUS in the treatment of gastric varices would be helpful. Exploring the best methods for surveillance after treatment of gastric varices is needed. Finally, comparisons of fibrin glue with other closure devices and treatment modalities for therapy of fistulae are needed.

SUMMARY

Tissue glues are used for control of bleeding and closure of fistulae and anastomotic leaks. Cyanoacrylate glues are effective at achieving initial hemostasis for bleeding gastric varices and are commonly used outside the United States, but this remains an off-label use in the United States. Future research demonstrating the safety and efficacy of these compounds may lead to wider adoption in this country.

DISCLOSURE

The authors disclosed no financial relationships relevant to this article.

Abbreviations: RCT, randomized, controlled trial; TIPS, transcutaneous intrahepatic portosystemic shunt.

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