TECHNOLOGY STATUS EVALUATION REPORT

Tissue adhesives and fibrin glues

NOVEMBER 2003

INTRODUCTION

To promote the appropriate use of new or emerging technologies, the American Society for Gastrointestinal Endoscopy Technology Committee has developed a series of status evaluation papers. This process presents relevant information about these technologies to practicing physicians for the education and the care of their patients. In many cases, data from randomized controlled trials are lacking and only preliminary clinical studies are available. Practitioners should continue to monitor the medical publications for subsequent data about the efficacy, safety, societal, and economic aspects of the technologies.

BACKGROUND

A variety of adhesive substances can be applied locally during surgery or endoscopy for hemostasis, wound closure, or fistula repair. The main classes of tissue adhesives are cyanoacrylate glues, fibrin glue, and thrombin. Cyanoacrylate glues are widely used in GI endoscopy outside of the United States for control of bleeding from gastric varices and, to a much lesser degree, for hemostasis of bleeding peptic ulceration and for closure of fistulas and anastomotic leaks. Fibrin glue (fibrinogen and thrombin) and thrombin have been used extensively in all surgical disciplines for tissue adhesion; suture support; hemostasis; wound care; and the sealing of body cavities, including the subarachnoid space; and endoscopically for the treatment of bleeding. Another class of agents, polysaccharide gels, are undergoing clinical trials for trauma-related, operative, and endoscopic hemostasis. This status evaluation report will review the described uses of cyanoacrylate glues, fibrin glue, and thrombin in GI endoscopy.

TECHNICAL CONSIDERATIONS

Cyanoacrylates

Cyanoacrylates are a class of synthetic glues that rapidly solidify upon contact with weak bases, such as water or blood.[1] A variety of cyanoacrylates are used for superficial wound closure.[2] N-butyl-2-cyanoacrylate (Histoacryl; B Braun, Melsungen, Germany) is the most commonly used cyanoacrylate glue for GI applications. Another N-butyl-2-cyanoacrylate (Glubran; GEM S.r.l., Viareggio, Italy) recently has been approved for endoscopic use in Europe. Neither Histoacryl nor Glubran are commercially available in the United States. The only U.S. Food and Drug Administration's approved agent is 2-octyl-cyanoacrylate (Dermabond; Ethicon, Inc., Somerville, N.J.), which has labeling indications for wound closure but not for endoscopic applications. This agent has a longer ester attached to the main compound and, hence, polymerizes more slowly.

When injected intravascularly, N-butyl-2-cyanoacrylate promptly solidifies, producing a cast of the vessel. Subtotal occlusion is immediate, and total occlusion occurs within hours.[3,4] Mild eosinophilic inflammation is present at 24 hours, and limited tissue reaction is present by day 7. In variceal applications, the cast of glue extrudes into the lumen after a week or two, generally without resultant bleeding. The variceal lumen remains patent, and variceal scarring or sclerosis is not evident.

One study compared the tissue effects of 2-octyl-cyanoacrylate (Dermabond) to that of N-butyl-2-cyanoacrylate (Histoacryl) in the auricular vein of rabbits.[4] Both were used in a 1:1 mixture with lipiodol. Polymerization of the octyl-cyanoacrylate was somewhat slower, and occlusion of the vein required larger volumes (0.5 vs. 0.2 mL) than with the butyl-cyanoacrylate. Histologic effects at 4 hours, 24 hours, and 7 days were essentially the same. This study concluded that higher volumes of Dermabond

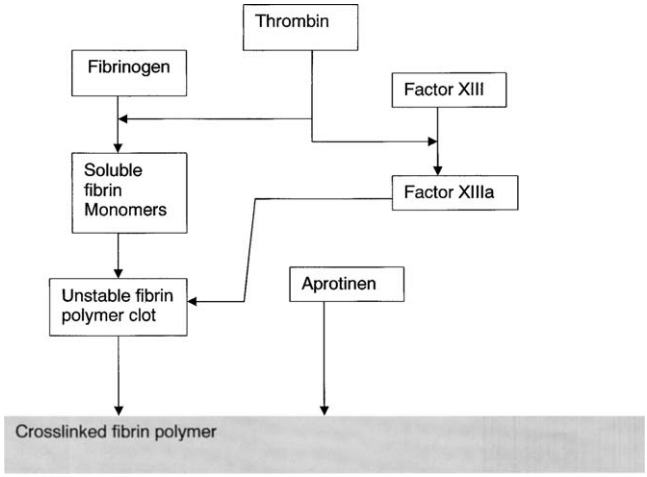

Figure 1. Schema of fibrinogen and thrombin interaction to yield a mature "fibrin glue" clot. (Adapted from Dunn, Drugs 1999).

would be required to produce an equivalent intravariceal effect to that of Histoacryl and that further studies are needed to determine the ideal dilutions and the dose response for Dermabond injection.

Mixing cyanoacrylate glues with the lipid soluble contrast agent lipiodol enhances radiopacity and retards the rate of solidification, thereby facilitating endoscopic administration via needle injection, while reducing the risk of inadvertent adherence to catheters and endoscopes. Various mixtures of Histoacryl and lipiodol have been advised, ranging from 1:1 to 1:1.6.[1] Over-dilution may increase the risk of embolization before the glue can solidify at the time of injection. Glubran polymerizes a little more slowly and, thus, does not require the use of lipiodol for injection. Varied dilutions of Dermabond and lipiodol have not been studied.

Fibrin glue and thrombin

Thrombin promotes the conversion of fibrinogen to fibrin, producing a local fibrin clot. Thrombin injected alone for hemostasis relies on the local presence and functionality of the patient's own fibrinogen and other products in the coagulation cascade to promote clotting. Formulations of fibrin glue contain two separate constituent component solutions, a substrate containing highly purified freeze-dried human fibrinogen and factor XIII and a starter solution containing human thrombin, which are admixed during administration. The thrombin component typically contains calcium and an antifibrinolytic agent (e.g., aprotinen) to prevent rapid fibrinolysis. The component solutions are reconstituted in two separate syringes with sterile water immediately before use. When mixed, these agents form a cell-free clot by mimicking the terminal phase of the physiologic clotting cascades, in which thrombin cleaves fibrinogen, yielding soluble fibrin monomers, which assemble first into loosely aggregated fibrils by hydrogen bonding and then into a stronger crosslinked fibrin polymer by covalent bonding. Thrombin also activates factor XIII, which, in the presence of calcium, facilitates the covalent bonding of the fibrin polymer (Fig. 1).[5] The speed of formation and the character of the clot vary among proprietary and locally produced fibrin glues, depending upon the relative concentrations of the components. Commercial preparations tend to be more highly purified and, hence, more predictable, stronger, and more durable than local blood-bank preparations. Fibrin glue is fully resorbed by macrophages and fibroblasts within 2 weeks of application.[6]

Fibrin glue is available from two commercial sources in the United States. Tisseel (Baxter, Westlake Village, Calif.) and Hemaseel (Hemacure, Sarasota, Fla.) are approved for topical application and sealing of anastomoses in cardiovascular and colorectal surgery. Nevertheless, fibrin glue is used in many other surgical specialties. While fibrin glues have been used in Europe for endoscopic hemostasis in bleeding ulcers and varices, in the United States, product labeling does not endorse intravascular injection.

Bovine thrombin, from varied commercial sources, has been used to enhance local clot formation via its effect on innate fibrinogen. It is approved for application in dry form or as a spray after reconstitution in sterile water or saline solution. While bovine thrombin has been used with some success, safety concerns relating to antibody development to factor V, anaphylaxis, and bovine spongiform encephalopathy, and the putative risk of Creutzfeldt-Jakob disease have tempered enthusiasm for this compound. Human-derived thrombin is available commercially and from local blood bank sources.

EFFICACY AND COMPARISON TO AVAILABLE TECHNOLOGIES

Cyanoacrylates for bleeding

There are several randomized controlled trials comparing use of cyanoacrylates (Histoacryl) to other therapies for treatment of esophageal varices.[7-9] Taken together, they demonstrate equivalency for arrest of acute bleeding and equivalency or superiority for prevention of recurrent bleeding with use of cyanoacrylate, with or without concurrent sclerotherapy, vs. treatment with traditional sclerosants alone.

The only randomized controlled trial of cyanoacrylate injection for gastric varices reported higher rates of initial hemostasis, a lower recurrent bleeding rate, lower treatment-induced ulcer bleeding, lower blood transfusion requirements, and lower mortality with butyl-cyanoacrylate than with serial banding.[10] There are no randomized prospective trials comparing cyanoacrylate injection with commonly used sclerosing agents for gastric varices. A prospective non-randomized trial[11] and numerous large case series report that Histoacryl injection controls acute gastric variceal bleeding in over 90% of patients and that serial treatment yields reduced recurrent bleeding and achieved obliteration in 70% to 90% of patients.[12-19] Based on these data, injection of cyanoacrylate has been widely adopted for treatment of bleeding gastric varices outside of the United States.

One study compared secondary prophylaxis via complete obliteration by using endoscopic injection of Histoacryl with long-term propranolol administration to prevent recurrent bleeding in patients with esophagogastric varices.[20] Early and late recurrent bleeding and early and overall deaths were equivalent; however, Histoacryl use was associated with a higher incidence of complications.

In the only randomized controlled trial of cyanoacrylate glue injection for hemostasis in gastroduodenal ulcer bleeding, Histoacryl and hypertonic saline solution injection[21] yielded equivalent rates of hemostasis, with the exception of a decreased recurrent bleeding rate in the subset of patients with active arterial bleeding treated with cyanoacrylate. However, two patients treated with Histoacryl developed systemic embolization, one of whom died.

Fibrin glue/thrombin for bleeding

Thrombin injection has been reported to be significantly better than no endoscopic therapy for bleeding gastroduodenal ulcers.[22] Several randomized controlled trials have compared injection of fibrin glue/thrombin, with other hemostatic modalities or injectable agents for treatment of bleeding gastroduodenal ulcers. However, these trials have considerable variability in treatment parameters and measured outcomes, and none evaluated the addition of fibrin glue to currently standard multimodality treatment when using epinephrine injection plus contact thermal probes, making blanket comparison difficult. Taken on the whole, these studies reported equivalent or greater efficacy with use of fibrin glue or thrombin injection compared with the study alternatives.[23-31] Notable among these trials, fibrin glue was evaluated in the largest trial ever conducted in the endoscopic treatment of upper-GI bleeding: 850 patients with active bleeding or a non-bleeding visible vessel at endoscopy were randomly assigned in an open-label, multicenter trial to single injection therapy with polidocanol, single application of fibrin glue, or daily fibrin glue until the visible vessel disappeared and the ulcer floor was clear or covered with hematin.[24] All patients received pretreatment with epinephrine. The patients who received multiple applications of fibrin sealant had significantly less recurrent bleeding than the polidocanol group (15% vs. 23%) and had fewer acute treatment failures (8% vs. 13%). The single fibrin glue treatment was not significantly better than the single polidocanol therapy. Secondary outcomes such as transfusions, surgeries, and deaths were not significantly different among the treatment groups. A potential but unproven benefit of thrombin and fibrin glue may be a decrease in the marked tissue injury caused by thermal devices and sclerosants.[32] They also may promote collagen deposition and healing of ulcers.

Fibrin glue has been injected for arrest of variceal bleeding[33,34] with marginal results. Thrombin also has been evaluated for use in endoscopic hemostasis of variceal bleeding. In a randomized trial in patients with acute esophageal variceal bleeding, sclerotherapy with ethanolamine plus human thrombin vs. sclerotherapy with ethanolamine alone yielded equivalent outcomes for all clinically important end points, including bleeding, coagulopathy, and mortality.[35] Two papers report retrospective experience with thrombin for bleeding gastric varices; acute hemostasis was achieved in 49 of 52 (94%) and in 9 of 12 (75%) of patients.[36,37] Recurrent bleeding occurred in 18% of 52 patients and 25% of 12 patients, with 8% overall bleeding related mortality in both groups.

There is a case report describing the effective use of fibrin glue in the endoscopic management of post-sphincterotomy bleeding in two cases.[38]

Miscellaneous clotting preparations for bleeding

Diffuse bleeding from intraluminal cancers often responds poorly to endoscopic therapy.[39] Soweid et al.[40] reported formation of an adherent coagulum and successful hemostasis in a patient with diffuse bleeding from a vascular cancer involving the rectum by topical application of 200 mL fresh frozen plasma plus 200 mL of saline solution containing 8000 U of bovine thrombin plus 8 mL of 10% calcium chloride. Another report described successful treatment of two patients with bleeding metastatic lesions in the upper GI tract by using a proprietary collagen-fibrin sealant (CoStasis Surgical Hemostat; Cohesion Inc., Palo Alto, Calif.).[41] In this system, a buffered calcium

chloride solution that contains bovine collagen and thrombin is combined during application with a bedside preparation of autologous platelet-rich plasma.

Cyanoacrylates for fistulas

Several published case series have described the use of cyanoacrylate glues for closure of intractable enterocutaneous fistulas[42-44]; however, this approach has not been critically evaluated nor widely adopted.

Fibrin glue for fistulas

Only a single randomized trial has evaluated the use of fibrin glue for closure of enterocutaneous fistulas.[45] Among 13 patients with persistent low-output fistulas after 2 to 4 weeks of conservative therapy with parenteral nutrition, 6 treated with instillation of 15 mL of fibrin glue closed within 4 days (mean 2 days), while 7 treated with continued conservative therapy closed only after 13 days ($p < 0.01$). Numerous case series report achieving prompt closure with use of fibrin glue for enterocutaneous,[46-50] anorectal,[51,52] and tracheo-esophageal[53] fistulas; esophageal perforations[54]; and leaking esophagoenteral anastomoses.[55] Patients with Crohn's disease generally respond less well. Several reports describe apparently advantageous use of transcutaneous fistuloscopy by using small-caliber instruments for delivery of the fibrin clot after clarification of complex anatomy and removal of exacerbating lesions, such as retained sutures.[56-58]

SAFETY

Complications associated with injection of cyanoacrylate glue for treatment of bleeding lesions include embolic events and equipment damage. Life-threatening complications have included episodes of abdominal, pulmonary, and intracerebral embolization and infarction.[59-68] In one study, cyanoacrylate injection of gastric varices yielded a 30% bacteremia rate, compared with a 6% rate among cirrhotics undergoing endoscopy for non-variceal bleeding.[69] The infectious agents correlated closely with those cultured from the accessory channels of the endoscopes. Instrument damage has included adhesion of the endoscope, adhesion of the needle with the varix, and obstruction of the injection catheter.[1]

Injection therapy with fibrin glue/thrombin is generally well tolerated. Previously reported complications related to its administration, including anaphylaxis, have been attributed primarily to the former use of bovine thrombin and aprotinen.[70] Antibodies against fibrinogen, factor V, and thrombin, in particular, and have led to serious coagulopathies and bleeding.[71] The conversion to human thrombin in fibrin glue preparations has significantly reduced but not fully abolished these reactions.[72] A complication, common to all blood components, is the potential transmission of an infectious disease, even from screened and tested blood. There has been one reported case of HIV transmission from fibrin sealant.[73] In addition to the patient, health care workers in the operating room may theoretically be exposed to an infectious disease risk when sealant is applied in an aerosolized form. Inadvertent intra-arterial injection of fibrin glue or thrombin may risk systemic embolization.[74]

Air embolization and death have occurred during fistuloscopy with injection of both cyanoacrylate and fibrin glues. This has been attributed to over-insufflation within the fistula track, caused by either fistuloscopy technique or use of a pressurized pneumatic spray system within the endoscope.[58] When treating aerodigestive fistulas from the GI end, there is a risk for tracheobronchial accumulation and airway plugging from overflow of excessive volumes of glue.

EASE OF USE

For cyanoacrylates, preparation and convenient arrangement of equipment and glue components before therapy is important for safe and efficient use. Extra personnel should be available to assist with the patient, the endoscope, the glue preparation, and the glue injection. Extra needle catheters should be available for the potential occurrence of needle occlusion by glue. Lipiodol is used to prime the interior of the injection needle catheter, the interior of the endoscope channel, and the tip of the endoscope. Lubricant gels or silicone also can be used to protect the endoscope and the accessory channel from accidental adhesion. Staff and patients should use protective eyewear or have their eyes draped during preparation and injection. The cyanoacrylates should be stored refrigerated at 2°C to 4°C.

When used for injection therapy of GI bleeding, the high viscosity of lipiodol requires the use of 2-mL syringes for injection. Individual injections are limited to volumes of 0.5 to 1.0 mL to minimize the risk of embolization. Steps for access, injection, and withdrawal from the lesion should be highly standardized. They include the following: care to avoid gravity dependent contamination of the endoscope, efficient tissue or variceal puncture, infusion of 1 cc of saline solution to ensure intravenous location (for variceal applications), injection of 0.5 to 1 cc of glue-lipiodol mixture, prompt subsequent injection of a volume of lipiodol or sterile water equivalent to

Table 1. CPT codes and RVU values for common endoscopic procedures with and without addition of injection therapy

Procedure	CPT	RVU	Medicare professional	APC facility
Esophagoscopy: diagnostic	43200	9.67	$110.85	$471.22
Esophagoscopy: injection	43201	6.65	$138.17	$471.22
EGD: diagnostic	43235	8.37	$142.81	$471.22
EGD: injection	43236	7.76	$172.16	$471.22
Colonoscopy: diagnostic	45378	11.93	$217.52	$499.85
Colon: injection	45381	10.56	$242.45	$499.85

CPT, Current procedural terminology; *RVU,* relative value units; *APC,* ambulatory procedure codes.

the dead space of the injection catheter, withdrawal of the needle catheter from the tissue, and continued flushing of water between variceal injections.[1]

Fibrin clot preparations may be dripped, injected, sprayed, or applied soaked in pledgets or sheets of absorbable gelatin sponge (Gelfoam; Pharmacia Corp., Peapack, N.J.). Because of the rapidity of clot formation, injection of the two major components usually is performed either sequentially or via a double-plunger syringe, which provides mixing while the agents are injected. Double-lumen injection needle catheters, which facilitate mixing just at the time of tissue entry, also are available for endoscopic applications. 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

Pharmacy costs for the commercially available fibrin glue available in the United states (Tisseel VH) vary by institution but are in the range of $82.00 per mL. Tisseel VH is packaged in 1-mL ($82), 2-mL ($164), and 5-mL ($410) kits, along with a dual-plunger syringe. Use of autologous or noncommercial monosource fibrin glue incurs significant blood banking costs for local manufacture and preparation. Thrombin comes in several forms. A vial of powder costs $163.00, a 5000-unit vial costs $55.00, and a 20,000-unit kit for application costs $175.00. Dermabond cyanoacrylate costs $238.80 per box of 12 ampules, altogether yielding approximately 5 mL of solution. Lipiodol is available from several vendors. Typical cost is $135.76 for a box of two 10-mL vials. Endoscopic applications of biologic or synthetic glues also may require use of a dual-plunger syringe and single- or dual-channel injection needles ($25-$50).

Injection of fibrin glue, or any other substance, is billed by using current procedural terminology (CPT) codes linked to the underlying procedure (Table 1); however, multiple therapies for a single lesion or problem cannot be billed concurrently. Hence, billing for injection plus thermal coagulation or clipping would only be reimbursed for the single highest charge modality.

SUMMARY

Synthetic and biologic tissue glues have been used for control of bleeding and closure of fistulas and anastomotic leaks. GI endoscopic applications of cyanoacrylate and fibrin glues are considered "off-label" uses. Embolization and death have been reported with cyanoacrylate injection for hemostasis. Embolization also can occur from intravascular injection of thrombin or fibrin glue. Fibrin glue/thrombin can induce antibody formation with subsequent coagulopathy; however, this is a rare event with use of human-source blood products. There are insufficient data to support routine endoscopic use of the available preparations of cyanoacrylate, fibrin glue, and thrombin in clinical practice.

REFERENCES

1. Seewald S, Sriram PVJ, Nagra M, Fennerty MB, Boyer J, Oberti F, et al. The expert approach: cyanoacrylate glue in gastric variceal bleeding. Endoscopy 2002;34:926-32.
2. Farion K, Osmond MH, Hartling L, Russell K, Klassen T, Crumley E, et al. Tissue adhesives for traumatic lacerations in children and adults. Cochrane Database Syst Rev [serial online] 2002;3:CD003326.
3. Fujiki K, Ohkusa T, Tamura Y, Sato C. Evaluation of the effects of esophageal varicosclerosants on local vascular occlusion and systemic blood coagulation. Gastrointest Endosc 1995;41:212-7.
4. Nguyen AJ, Baron TH, Burgart LJ, Leontovich O, Rajan E, Gostout CJ. 2-Octyl-cyanoacrylate (Dermabond), a new glue for variceal injection therapy: results of a preliminary animal study. Gastrointest Endosc 2002;55:572-5.
5. Dunn CJ, Goa KL. Fibrin sealant. A review of its use in surgery and endoscopy. Drugs 1999;58:863-86.
6. Pescatore P, Verbeke C, Harle M, Manefold BC. Fibrin sealing in peptic ulcer bleeding: the fate of the clot. Endoscopy 1998;30:519-23.
7. Omar MM, Fakhry SM, Mostafa I. Immediate endoscopic injection therapy of bleeding oesophageal varices: a prospective comparative evaluation of injecting materials in Egyptian patients with portal hypertension. J Egypt Soc Parasitol 1998;28:159-68.
8. Sung JJ, Yeo W, Suen R, Lee YT, Chung SC, Chan FK, et al. Injection sclerotherapy for variceal bleeding in patients with hepatocellular carcinoma: cyanoacrylate versus sodium tetradecyl sulphate. Gastrointest Endosc 1998;47:235-9.
9. Maluf-Filho F, Sakai P, Ishioka S, Matuguma SE. 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.
10. Lo GH, Lai KH, Cheng JS, Chen MH, Chiang HT. A prospective, randomized trial of butyl cyanoacrylate injection versus band ligation in the management of bleeding gastric varices. Hepatology 2001;33:1060-4.
11. Oho K, Iwao T, Sumino M, Toyonaga A, Tanikawa K. Ethanolamine oleate versus butyl cyanoacrylate for bleeding gastric varices: a nonrandomized study. Endoscopy 1995;27: 349-54.
12. Soehendra N, Nam VC, Grimm H, Kempeneers I. Endoscopic obliteration of large esophagogastric varices with bucrylate. Endoscopy 1986;18:25-6.
13. Dhiman RK, Chawla Y, Taneja S, Biswas R, Sharma TR, Dilawari JB. Endoscopic sclerotherapy of gastric variceal bleeding with N-butyl-2-cyanoacrylate. J Clin Gastroenterol 2002;35:222-7.
14. Iwase H, Maeda O, Shimada M, Tsuzuki T, Peek RM Jr, Nishio Y, et al. Endoscopic ablation with cyanoacrylate glue for isolated gastric variceal bleeding. Gastrointest Endosc 2001;53:585-92.
15. Kind R, Guglielmi A, Rodella L, Lombardo F, Catalano F, Ruzzenente A, et al. Bucrylate treatment of bleeding gastric varices: 12 years' experience. Endoscopy 2000;32:512-9.
16. D'Imperio N, Piemontese A, Baroncini D, Billi P, Borioni D, Dal Monte PP, et al. Evaluation of undiluted N-butyl-2-cyanoacrylate in the endoscopic treatment of upper gastrointestinal tract varices. Endoscopy 1996;28:239-43.
17. Soehendra N, Grimm H, Nam VC, Berger B. N-butyl-2-cyanoacrylate: a supplement to endoscopic sclerotherapy. Endoscopy 1987;19:221-4.
18. Huang YH, Yeh HZ, Chen GH, Chang CS, Wu CY, Poon SK, 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.
19. Akahoshi T, Hashizume M, Shimabukuro R, Tanoue K, Tomikawa M, Okita K, et al. Long-term results of endoscopic Histoacryl injection sclerotherapy for gastric variceal bleeding: a 10-year experience. Surgery 2002;131:S176-81.
20. Evrard S, Dumonceau JM, Delhaye M, Golstein P, Deviere J, Moine OL. Endoscopic Histoacryl obliteration vs. propranolol in the prevention of esophagogastric variceal rebleeding: a randomized trial. Endoscopy 2003;35:729-35.
21. Lee KJ, Kim JH, Hahm KB, Cho SW, Park YS. Randomized trial of N-butyl-2-cyanoacrylate compared with injection of hypertonic saline-epinephrine in the endoscopic treatment of bleeding peptic ulcers. Endoscopy 2000;32:505-11.
22. Juszkiewicz P, Wajda Z, Dobosz M, Babicki A, Marczewski R. The role of endoscopic thrombin injections in the treatment of gastroduodenal bleeding. S Afr J Surg 1993;31:98-102.
23. Berg PL, Barina W, Born P. Endoscopic injection of fibrin glue versus polidocanol in peptic ulcer hemorrhage: a pilot study. Endoscopy 1994;26:528-30.
24. Rutgeerts P, Rauws E, Wara P, Swain P, Hoos A, Solleder E, et al. Randomised trial of single and repeated fibrin glue compared with injection of polidocanol in treatment of bleeding peptic ulcer. Lancet 1997;350:692-6.
25. Pescatore P, Jornod P, Borovicka J, Pantoflickova D, Suter W, Meyenberger C, et al. Epinephrine versus epinephrine plus fibrin glue injection in peptic ulcer bleeding: a prospective randomized trial. Gastrointest Endosc 2002;55:348-53.
26. Song SY, Chung JB, Moon YM, Kang JK, Park IS. Comparison of the hemostatic effect of endoscopic injection with fibrin glue and hypertonic saline-epinephrine for peptic ulcer bleeding: a prospective randomized trial. Endoscopy 1997;29:827-33.
27. Heldwein W, Avenhaus W, Schonekas H, Kaess H, Muller-Lissner S, Hasford B, et al. Injection of fibrin tissue adhesive versus laser photocoagulation in the treatment of high risk bleeding peptic ulcers: a controlled randomized study. Endoscopy 1996;28:756-60.
28. Koyama T, Fujimoto K, Iwakiri R, Sakata H, Sakata Y, Yamaoka I, et al. Prevention of recurrent bleeding from gastric ulcer with a non bleeding visible vessel by endoscopic injection of absolute ethanol: a prospective, controlled trial. Gastrointest Endosc 1995;42:128-31.
29. Benedetti G, Sablich R, Lacchin T. Endoscopic injection sclerotherapy in non-variceal upper gastrointestinal bleeding. Surg Endosc 1991;5:28-30.
30. Balanzo J, Villanueva S, Sainz J, Espoinos JC, Mendez C, Guarner C, et al. Injection therapy of bleeding peptic ulcer. Randomized trial using adrenaline and thrombin. Endoscopy 1990;20:157-9.
31. Kubba AK, Murphy W, Palmer KR. Endoscopic injection for bleeding peptic ulcer: a comparison of adrenaline alone with adrenaline plus human thrombin. Gastroenterology 1996; 111:623-8.
32. Laine L. Endoscopic therapy for bleeding ulcers: room for improvement [editorial]? Gastrointest Endosc 2003;57: 557-60.
33. Datta D, Vlavianos P, Alisa A, Westaby D. Use of fibrin glue (Beriplast) in the management of bleeding gastric varices. Endoscopy 2003;35:675-8.
34. 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.
35. Kitano S, Hashizume M, Yamaga H, Wada H, Iso Y, Iwanaga T, et al. Human thrombin plus 5 percent ethanolamine oleate injected to sclerose oesophageal varices: a prospective randomized trial. Br J Surg 1989;76:715-8.
36. Przemioslo RT, McNair A, Williams R. Thrombin is effective in arresting bleeding from gastric variceal hemorrhage. Dig Dis Sci 1999;44:778-81.
37. Yang WL, Tripathi D, Therapondos G, Todd A, Hayes PC. Endoscopic use of human thrombin in bleeding gastric varices. Am J Gastroenterol 2002;97:1381-5.
38. Born P, Ott R, Rosch T. Endoscopic hemostasis using fibrin sealant for postsphincterotomy bleeding: report of two cases. Gastrointest Endosc 2000;51:731-3.
39. Loftus EV, Alexander GL, Ahlquist DA, Balm RK. Endoscopic treatment of major bleeding from advanced gastroduodenal malignant lesions. Mayo Clin Proc 1994;69:736-40.
40. Soweid AM, Presti ME, Saeed AZ. Intrarectal fibrin glue: a novel method of hemostasis for bleeding from rectal tumor. Gastroint Endosc 1997;45:427-9.
41. Milkes DE, Friedland S, Lin OS, Reid TR, Soetikno RM. A novel method to control severe upper GI bleeding from metastatic cancer with a hemostatic sealant: the CoStasis surgical hemostat. Gastroint Endosc 2002;55:735-40.
42. Lee YC, Na HG, Suh JH, Park IS, Chung KY, Kim NK. Three cases of fistulae arising from gastrointestinal tract treated with endoscopic injection of Histoacryl. Endoscopy 2001;33: 184-6.
43. Gdanietz K, Krause I. Plastic adhesives for closing esophagotracheal fistulae in children. Z Kinderchir 1975;17:137-8.
44. Seewald S, Groth S, Sriram PVJ, Xikun H, Akaraviputh T, Mendoza G, et al. Endoscopic treatment of biliary leakage

with N-butyl-2 cyanoacrylate. Gastrointest Endosc 2002;56: 916-9.
45. Hwang TL, Chen MF. Randomized trial of fibrin tissue glue for low output enterocutaneous fistula. Br J Surg 1996; 83:112.
46. Eleftheriadis E, Tzartinoglou E, Kotzampassi K, Aletras H. Early endoscopic fibrin sealing of high-output postoperative enterocutaneous fistulae. Acta Chir Scand 1990;156:625-8.
47. Rabago LR, Ventosa N, Castro JL, Marco J, Herrera N, Gea F. Endoscopic treatment of postoperative fistulae resistant to conservative management using biological fibrin glue. Endoscopy 2002;34:632-8.
48. Papavramidis ST, Eleftheriadis EE, Apostolidis DN, Kotzampassi KE. Endoscopic fibrin sealing of high-output nonhealing gastrocutaneous fistulae after vertical gastroplasty in morbidly obese patients. Obes Surg 2001;11:766-9.
49. Cellier C, Landi B, Faye A, Wind P, Frileux P, Cugnenc PH, et al. Upper gastrointestinal tract fistulae: endoscopic obliteration with fibrin sealant. Gastrointest Endosc 1996;44: 731-3.
50. Shand A, Pendlebury J, Reading S, Papachrysostomou M, Ghosh S. Endoscopic fibrin sealant injection: a novel method of closing a refractory gastrocutaneous fistula. Gastrointest Endosc 1997;46:357-8.
51. Venkatesh KS, Ramanujam P. Fibrin glue application in the treatment of recurrent anorectal fistulae. Dis Colon Rectum 1999;42:1136-9.
52. Sentovich SM. Fibrin glue for anal fistulas: long-term results. Dis Colon Rectum 2003;46:498-502.
53. Willetts IE, Dudley NE, Tam PKH. Endoscopic treatment of recurrent tracheo-oesophageal fistulae: long-term results. Pediatr Surg Int 1998;13:256-8.
54. Fernandez FF, Richter A, Freudenberg S, Wendl K, Manegold BC. Treatment of endoscopic esophageal perforation. Surg Endosc 1999;13:962-6.
55. Pross M, Manger T, Reinheckel T, Mirow L, Kunz D, Lippert H. Endoscopic treatment of clinically symptomatic leaks of thoracic esophageal anastomoses. Gastrointest Endosc 2000; 51:73-6.
56. Wong SKH, Lam YH, Lau JYW, Lee DWH, Chan ACW, Chung SCS. Diagnostic and therapeutic fistuloscopy: an adjuvant management in postoperative fistulae and abscesses after upper gastrointestinal surgery. Endoscopy 2000;32: 311-3.
57. Kurokawa T, Okushiba S, Kadoya M, Miyamoto D, Kurashima Y, Kitagami H, et al. Selective occlusion with fibrin glue under fistuloscopy: seven cases of postoperative management for intractable complex fistulae. Endoscopy 2002; 34:220-2.
58. Lange V, Meyer G, Wenk H, Schildberg FW. Fistuloscopy: an adjuvant technique for sealing gastrointestinal fistulae. Surg Endosc 1990;4:212-6.
59. Lee GH, Kim JH, Lee KJ, Yoo BM, Hahm KB, Cho SW, et al. Life-threatening intraabdominal arterial embolization after Histoacryl injection for bleeding gastric ulcer. Endoscopy 2000;32:422-4.
60. Palejwala AA, Smart HL, Hughes M. Multiple pulmonary glue emboli following gastric variceal obliteration. Endoscopy 2000;32:S1-2.
61. Cheng PN, Sheu BS, Chen CY, Chang TT, Lin D. Splenic infarction after Histoacryl injection for bleeding gastric. Gastrointest Endosc 1998;48:426-7.
62. Gallet B, Zemour G, Saudemont JP, Renard P, Hillion ML, Hiltgen M. Echocardiographic demonstration of intracardiac glue after endoscopic obliteration of gastroesophageal varices. J Am Soc Echocardiogr 1995;8:759-61.
63. See A, Florent C, Lamy P, Levy VG, Bouvry M. [Cerebrovascular accidents after endoscopic obturation of esophageal varices with isobutyl-2-cyanoacrylate in 2 patients] [French]. Gastroenterol Clin Biol 1986;10:604-7.
64. Turler A, Wolff M, Dorlars D, Hirner A. Embolic and septic complications after sclerotherapy of fundic varices with cyanoacrylate. Gastrointest Endosc 2001;53:228-30.
65. Tan YM, Goh KL, Kamarulzaman A, Tan P, Ranjeev P, Salem O, et al. Multiple systemic embolisms with septicemia after gastric variceal obliteration with cyanoacrylate. Gastrointest Endosc 2002;55:276-8.
66. Roesch W, Rexroth G. Pulmonary, cerebral and coronary emboli during bucrylate injection of bleeding fundic varices. Endoscopy 1998;30:S89-90.
67. Tsokos M, Bartel A, Schoel R, Rabenhorst G, Schwerk WB. Fatal pulmonary embolism after endoscopic embolization of downhill esophageal varix. Dtsch Med Wochenschr 1998;123: 691-5.
68. Cheng PN, Sheu BS, Chen CY, Chang TT, Lin ZX. Splenic infarction after Histoacryl injection for bleeding gastric varices. Gastrointest Endosc 1998;48:426-7.
69. Chen WC, Hou MC, Lin HC, Yu KW, Lee FY, Chang FY, et al. Bacteremia after endoscopic injection of N-butyl-2-cyanoacrylate for gastric variceal bleeding. Gastrointest Endosc 2001;54:214-8.
70. Spotnit WE. Fibrin sealant in the United States: clinical use at the University of Virginia. Thromb Haemost 1995;74: 482-5.
71. Ortel TL, Charles LA, Keller FG, Marcom PK, Oldham HN Jr, Kane WH, et al. Topical thrombin and acquired coagulation factor inhibitors: clinical spectrum and laboratory diagnosis. Am J Hematol 1994;45:128-35.
72. Caers J, Reekmans A, Jochmans K, Naegels S, Mana F, Urbain D, et al. Factor V inhibitor after injection of human thrombin (Tissucol) into a bleeding peptic ulcer. Endoscopy 2003;35:542-4.
73. Wilson SM, Pell P, Donegan EA. HIV-1 transmission following the use of cryoprecipitated fibrinogen as gel/adhesive [abstract]. Transfusion 1991;31:51S.
74. Baxter Healthcare. Tissue sealing. [cited 2003 Feb 5]. Available from: URL:http://www.tissuesealing.com/us/products/biological/monograph.cfm

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