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Techniques in Gastrointestinal Endoscopy

Tissue Adhesives: A Review

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Tissue adhesives represent a group of natural and artificial compounds that are currently used for a variety of local applications including hemostasis, wound closure, and fistula repair. The most commonly utilized tissue adhesives in GI endoscopy include cyanoacrylates, fibrin glues, and thrombin. Other adhesives, such as collagen-based sealants and PEG polymers, are beginning to be studied in various surgical disciplines and may one day find a role in endoscopic practice as well. This review covers the endoscopic use of available tissue adhesives and highlights pertinent technical considerations.

KEYWORDS endoscopy tissue adhesives, cyanoacrylates, fibrin glues, glutaraldehyde, hydrogels, collagen-based glues

Tissue adhesives represent a group of compounds that can be applied locally for a variety of indications, including hemostasis, wound closure, and fistula repair. The main classes of tissue adhesives currently utilized in GI endoscopy include cyanoacrylates, fibrin glues, and thrombin. Cyanoacrylates are used widely outside of the United States for gastric variceal bleeding and, to a lesser extent, ulcer bleeding and fistula closures. For the time being, their GI endoscopic applications remain an "off-label" use in the United States. Fibrin glues and thrombin are used extensively in various surgical disciplines, but have only been employed recently in GI endoscopy, primarily for hemostasis and fistula closure. In addition, other glues, such as collagen-based adhesives and PEG polymers, are beginning to be studied.

Cyanoacrylates

Background

Cyanoacrylates are synthetic glues that rapidly polymerize on contact with water or blood.[1] N-butyl-2-cyanoacrylate (Histoacryl; B Braun, Melsungen, Germany) has been used extensively in endoscopic therapy for the last 10 years. Another N-butyl-2-cyanoacrylate (Glubran; GEM S.r.l., Viareggio, Italy) was recently approved for endoscopic use in Europe. Neither Histoacryl nor Glubran is commercially available in the United States at this time.[2] 2-Octyl-cyanoacrylate (Dermabond; Ethicon, Inc., Somerville, NJ), approved by the Federal Drug Administration for superficial wound closure, is widely used by emergency room physicians, dermatologists, and plastic surgeons.[3]

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Clinical Applications

Gastric Variceal Bleeding

Injection therapy with cyanoacrylates is now considered the first-line endoscopic intervention for bleeding gastric varices as well as secondary prevention of gastric variceal bleeds outside of the United States.[4] In a randomized controlled trial of 59 patients, cyanoacrylate injection of bleeding gastric varices was reported to be more effective and safer than band ligation. Both initial hemostatic rate and rebleeding rates were lower in the cyanoacrylate group compared with the band ligation group. Initial hemostatic rates were 87% in the cyanoacrylate group compared with 45% in the band ligation group ($P = 0.03$); rebleeding rates in the cyanoacrylate group were 31% compared with 54% in the band ligation group ($P = 0.0005$). Treatment-induced ulcer bleeding occurred in two patients (7%) in the cyanoacrylate group and eight patients (28%) in the band ligation group ($P = 0.03$). The amount of blood transfusions required were also higher in the band ligation group than in the cyanoacrylate group (4.2 ± 1.3 vs 2.6 ± 0.9 units, respectively) ($P < 0.01$).[5]

Results of a nonrandomized study and several large case series suggest that Histoacryl is superior to sclerotherapy in the management of patients with gastric variceal bleeding. Histoacryl controls acute gastric variceal bleeding in over 90% of subjects, and serial treatment achieves variceal obliteration and decreases re-bleeding in 70% to 90% of patients.[6-14]

Esophageal Variceal Bleeding

Several randomized controlled studies have demonstrated that injection of cyanoacrylate is comparable to sclerotherapy in the endoscopic hemostasis of acute variceal bleeding and prevention of rebleeding.[15-17] However, there have been no trials comparing cyanoacrylate therapy to endoscopic band ligation, which is widely accepted as the treatment of choice for esophageal varices.

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Peptic Ulcer Bleeding

In a randomized controlled trial comparing injection of cyanoacrylate and hypertonic saline for bleeding gastroduodenal ulcers, initial hemostasis was similar in both groups and the rebleeding rate was lower after cyanoacrylate injection.[18] There are no studies comparing glue injection to a combination of injection and cautery or application of clips, which are considered more effective than saline injection alone for the treatment of bleeding ulcers.

Bleeding from Other Sources

Cyanoacrylate injection has been used successfully in the management of a few patients with Dieulafoy's lesions and bleeding tumors.[19,20]

Closure of Fistula

Cyanoacrylates have been shown to be successful in the closure of pancreatic fistulas, biliary fistulas,[21] and gastrointestinal fistulas.[22] Seewald and coworkers reported successful closure of pancreatic fistulas in 8 of 12 patients using endoscopic injection of Histoacryl into the fistulous tract and endoscopic drainage.[23] Seven of the 8 successful patients required only 1 treatment over a median follow-up period of 21 months. Closure was temporary in 2 patients, unsuccessful in 1 patient, and there was 1 death within 24 hours of treatment from pulmonary embolism.

Technical Considerations

Mechanism of Action

Histological studies reveal that intravascular injection of N-butyl-2-cyanoacrylate produces an immediate cast of the vessel. Total occlusion of the vessel occurs within hours. Mild eosinophilic inflammation is observed at 24 hours. By day 7, tissue reaction is minimal. After 1 to 2 weeks, the cyanoacrylate casts extrudes into the lumen, leaving behind a patent variceal lumen generally without re-bleeding. Variceal scarring or sclerosis is usually absent.[24]

Preparation

The potency (ie, "stickiness") of cyanoacrylates necessitates dilution before application. Most endoscopists mix cyanoacrylates with the lipid soluble lipiodol to retard polymerization and enhance imaging. Various mixtures of Histoacryl and lipiodol (range: 1:1 to 1:1.6) have been recommended.[1] Whereas a mixture that is too concentrated risks premature polymerization, a mixture too dilute increases the risk of embolization. Glubran, by comparison, polymerizes slowly and therefore does not require dilution. Although Dermabond is weak in polymerization compared with Histoacryl, it requires dilution with lipiodol. An ideal dilutional range has not yet been ascertained.[2] Lipiodol is also used to coat the interior of the injection needle catheter, the interior of the endoscope channel, and the tip of the endoscope to avoid damage to the endoscope. An injection catheter with a hub resistant to glue-induced dissolution (eg, 23- to 25-gauge needle, model #LDVI-23/25-MH; Wilson-Cook Medical Inc., Winston-Salem, NC) is also a necessity.[25]

Application

All staff should use protective eyewear, and patients should have their eyes draped. Individual injections should be slow. It should be limited to 0.5 to 1.0 mL to minimize the risk of embolization. Some investigators suggest a test injection of 1.0 mL of normal saline to verify intravenous location. Following cyanoacrylate injection, an equivalent volume of saline or lipiodol may be used to fill the dead space of the injection catheter and deliver the remaining glue. Obliteration of varices can be assessed by blunt probe palpation, EUS to demonstrate hypoechoic vascular channels, and concurrent fluoroscopy to take advantage of the radiopacity of lipiodol.[26]

Complications

In general, five types of complications have been described with the use of cyanoacrylates. Although there are no studies that report the rate of individual complications, they are nevertheless presented in order of frequency as described in the literature. These include a systemic inflammatory reaction to foreign body, ie, pain and fever, local tissue necrosis and inflammatory reaction to foreign body (mediastinitis, esophageal pleural fistula, duodenal ulcer perforation, pancreaticoduodenal necrosis, inflammatory pseudotumor of pancreatic tail),[27-31] thrombo-embolic complications (splenic, portal, pulmonary, coronary, cerebral, and inferior vena cava),[32-34] and septic complications.[35] In addition, adherence of the needle to wall of varix and occlusion of the sclerotherapy catheter by residual adhesive have been reported.[36]

Fibrin Sealants

Background

Fibrin sealants or "fibrin glues," the end product of coagulation cascade, serve as a primary hemostatic plug as well as a matrix to enhance wound healing. Two types of fibrin sealants are available on the market: 1) P*urified thrombin* promotes the conversion of the patient's own fibrinogen to fibrin; and 2) a combination of a highly purified *mixture of human fibrinogen+ factor XIII* and *human thrombin solution* [contains calcium and aprotinen (antifibrinolytic agent)]. These two components are then combined during administration to yield a fibrin clot. In the United States, fibrin glue is available from two commercial sources: Tisseel (Baxter, Westlake Village, CA) and Hemaseel (Hemacure, Sarasota, FL). Additionally, bovine thrombin is available from many commercial enterprises, and human thrombin is available from both commercial sources and local blood banks.[37]

In contrast to synthetic adhesives, fibrin sealants have the advantage of being biocompatible and biodegradable. The fibrin clot is resorbed within days to weeks as a part of the normal wound-healing process. As such, they are not associated with inflammation, foreign body reactions, tissue necrosis, or extensive fibrosis.[38]

Clinical Applications

General Applications

Both fibrin glue and thrombin have been used extensively since the 1970s for hemostasis in cardiac surgery,[39] for sealing of vascular grafts and treatment of aortic dissections in vascular surgery,[40] for treatment of broncho-pleural fistulas in thoracic surgery,[41] for treatment of hemorrhage, biliary leakage, and exocrine secretions in hepatobiliary,[42] and pancreatic surgery,[43] and for sealing of CSF leakage in neurosurgery.[44]

GI Applications: Hemostasis

GI endoscopists started utilizing fibrin sealants in the early 1990s. The fibrin glue has been shown to be effective in the treatment of bleeding gastroduodenal ulcers. In a large open-label multicenter trial of endoscopic management of bleeding gastroduodenal ulcers, 850 patients were randomized to a single injection of polidocanol, single application of fibrin glue, or repeated fibrin glue injection until the disappearance of visible vessel. All the lesions were injected with epinephrine before injection of polidocanol or fibrin glue. Multiple applications of fibrin sealant resulted in a significant reduction of rebleeding (15% vs 23%) and fewer treatment failures (8% vs 13%) compared with the polidocanol group. However, single treatment fibrin sealant was not significantly better than single polidocanol therapy.[45]

Compared with thermal devices and sclerosants, fibrin sealants may cause less tissue injury, and promote collagen deposition and ulcer healing, which is an attractive feature in the management of patients who require anticoagulation.[46]

Fibrin sealants have been used for both esophageal and gastric variceal bleeding with marginal results.[47,48] Likewise, thrombin has yielded equivocal results as a hemostatic agent in variceal hemorrhage. In a randomized trial of patients with acute esophageal variceal bleeding, sclerotherapy (ethanolamine) was comparable to a combination of sclerotherapy and human thrombin in terms of hemostasis, coagulopathy, and mortality.[49] In 2 retrospective studies of thrombin injection for gastric variceal bleeding, acute hemostasis was reported in 49 of 52 patients (94%) and in 9 of 12 patients (75%), respectively; rebleeding was observed in 18 of 52 patients (18%) and 3 of 12 patients (25%), respectively.[50,51]

Fibrin glue injection has also been used in the endoscopic management of postsphincterotomy bleeding and postpolypectomy bleeding.[52,53]

GI Applications: Closure of Perforations, Fistulae, and Anastomotic Leaks

Fibrin sealants have been shown to be valuable in closure of fistulas. Only one randomized controlled trial has been performed for closure of enterocutaneous fistulas. Thirteen patients with low-output fistulas on parenteral nutrition for 2 to 4 weeks were randomized to installation of 15 mL of fibrin glue (6 patients) or continued conservative therapy (7 patients). Fistulas closed early in the fibrin-treated group compared with controls (4 days vs 13 days, $P < 0.01$).[54]

Fibrin glue application has also been shown to be successful in the closure of anorectal fistula,[55] tracheo-esophageal fistulas,[56] esophageal perforations,[57] and leaking esophagoenteral anastomoses.[58]

Technical Considerations

Individual elements are heated in custom heating units for up to 20 minutes before their use. Fibrin sealants tend to polymerize rapidly. Hence, the individual components are either applied sequentially or simultaneously through a double-plunger syringe or a double-lumen injection needle catheter. Premature clotting can occlude injection catheters, particularly single-channel varieties. Fibrin glue injection does not damage the endoscope.[2]

Complications

Fibrin sealant injection is usually well tolerated. Aside from the risk of embolization, it is associated with complications related to the use of a biological compound. Anaphylaxis has been reported as a rare complication of bovine thrombin and aprotinen,[59] but human fibrin glue/thrombin is generally well tolerated. Serious bleeding diatheses have resulted from antibody formation against fibrinogen, factor V, and thrombin from both human and bovine sources.[60] Finally, the risk of viral transmission has been a subject of much debate, particularly with one early report of HIV transmission and a recent surgical report of parvovirus transmission attributed to fibrin sealant use.[61,62] However, current screening and viral reduction and inactivation processes render this risk exceedingly small in commercial preparations. Single-donor source fibrin sealants are preferable to reduce the risk of viral transmission. Furthermore, recombinant human thrombin (rhThrombin) is currently being studied in Phase II trials for topical hemostasis in surgical patients.[63]

Collagen-Based Adhesives

Collagen-based adhesives represent a relatively new class of tissue glues. Two agents have been approved for use in the United States: FloSeal (Sulzer Spine-tech, Anaheim, CA) and Proceed (Fusion Medical Technologies, Mountain View, CA). These two products are chemically identical compounds: a combination of bovine thrombin and bovine collagen, which provides the matrix for the clot. FloSeal is marketed for hemostasis in vascular surgery, whereas Proceed is intended for prevention and treatment of CSF leaks.[37] Currently, there are no published reports of endoscopic applications of either FloSeal or Proceed.

Another novel collagen product is CoStasis (Cohesion Technologies, Inc., Palo Alto, CA), which uses a combination of autologous human plasma obtained from patient's blood and a mixture of bovine collagen and thrombin. It is used as a spray for surgical hemostasis. CoStasis has been successfully used for endoscopic control of severe upper gastrointestinal bleeding from metastatic cancer.[64]

Hydrogels (Polyethylene Glycol Polymers)

Polyethylene glycol (PEG) polymers are hydrogels that are used for tissue adhesion. FocalSeal-L (Genyzme Biosurgery, Inc., Cambridge, MA; FDA approved) is a water-soluble, bioabsorbable compound that requires a significant amount of time for photoactivation, which is a limitation for its use in hemostasis. Another PEG polymer, CoSeal (Cohesion Technologies), does not require the same activation source and is currently being used in Europe for similar purposes. FocalSeal has thus far proved useful in decreasing air leaks after major thoracic surgery but has not yet been used in the GI endoscopic domain.[37]

Albumin-Based Compounds (Glutaraldehyde Glues)

This last group of adhesives is based on the combination of albumin and adhesion compounds. They are sometimes re-

ferred to in the literature as gelatin-resorcinol-formaldehyde-glutaraldehyde (GRFG) glues. Currently, there is one such compound approved in the United States called BioGlue (CryoLife, Inc., Kennesaw, GA), which is a combination of bovine albumin and glutaraldehyde glue. Currently it is limited to repair of aortic dissection (ie, filling in of the false lumen).[37] Its use in GI endoscopy has yet to be reported.

Future Direction

The use of tissue adhesives within gastrointestinal endoscopy is emerging from its nascent stages. Thus far, most of the focus has been on hemostasis and tissue sealing (ie, addressing leaks and fistulas). However, the potential for other applications remains large. For example, tissue adhesives stand to contribute as suture support in minimally invasive endoscopic surgery.[65] They also have the potential to serve as delivery systems. Tissue adhesives could conceivably be engineered for slow, localized release of pain medications, antibiotics, chemotherapy, growth factors, and actual cell lines.[66] The future of tissue adhesives can be as broad as the imagination.

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