

Sclerosing agents for use in GI endoscopy

The American Society for Gastrointestinal Endoscopy (ASGE) Technology Committee provides reviews of existing, new, or emerging endoscopic technologies that have an impact on the practice of gastrointestinal endoscopy. Evidence-based methodology is used, with a MEDLINE literature search to identify pertinent clinical studies on the topic and a MAUDE (Manufacturer and User Facility Device Experience Database [Food and Drug Administration Center for Devices and Radiological Health]) database search to identify the reported complications 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, and are reviewed and edited by the committee as a whole, and then 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 November 2006 by using the following key phrases: “esophageal varices,” “gastric varices,” “gastrointestinal bleeding,” “gastrointestinal fistula,” and “sclerosing solutions.” The commonly used sclerosing agents were also used as key words. Permutations of these keywords and phrases were performed to narrow the search. Additional references were obtained from the bibliographies of identified articles and through an Internet search engine. Emphasis was given, in all cases, to randomized controlled trials and, when necessary, to review articles from recognized experts. Finally a search of the MAUDE database was made for reported adverse events. Practitioners should continue to monitor the medical literature for subse-

quent data about the efficacy, safety, and socioeconomic aspects of these technologies.

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BACKGROUND

Endoscopic sclerotherapy, a well-established treatment for bleeding GI varices, accomplishes vascular obliteration by injection of a sclerosing agent. Crafoord and Frenckner introduced the concept in 1939, by using quinine to sclerose bleeding esophageal varices.¹ Sclerotherapy was the standard endoscopic therapy for bleeding varices in the United States until it was largely replaced by variceal band ligation, which proved to be safer and equally efficacious.² However, in many regions of the world, endoscopic sclerotherapy may still be the treatment of choice for acute variceal bleeding. This report reviews the indications, efficacy, safety, and costs of the commonly used sclerosants in GI endoscopic practice.

TECHNICAL CONSIDERATIONS

Sclerosants are tissue irritants that cause vascular thrombosis and endothelial damage, leading to endofibrosis and vascular obliteration when injected into or adjacent to blood vessels.³ Most sclerosants are fatty-acid derivatives or synthetic chemicals; others include alcohols and sugars (Table 1).¹ The most commonly used sclerosants are the synthetic chemicals sodium tetradecyl sulfate and polidocanol; the fatty-acid derivatives sodium morrhuate and ethanolamine oleate; and the alcohol ethanol.

Sodium tetradecyl sulfate

Sodium tetradecyl sulfate is 7-ethyl-2-methyl-4-hendecanol sodium sulfate (C₁₄H₂₉NaSO₄). It is a synthetic anionic surfactant that is available as 1% and 3% aqueous solutions with 2% benzyl alcohol and is buffered to a pH of 7.9 with sodium phosphate.^{1,4} It is packaged in 2-mL

TABLE 1. Sclerosants

Agent	Volume, mL per site/mL per session	Relative tissue injury	Availability in United States	Cost*
Fatty-acid derivatives				
Ethanolamine oleate, 5% (Ethamolin, QOL Medical, Inc, Woodinville, Wash)	1.5–5/20	+++	Yes	\$78.28 per 2-mL ampule
Sodium morrhuate, 5% (Scleromate, Glenwood LLC, Englewood, NJ)	0.5–5/15	+++	Yes	\$48.19 per 50-mg vial
Synthetic agents				
Sodium tetradecyl sulfate, 1% and 3% (Sotradecol, Bioniche Life Sciences, LLC, Belleville, Ontario, Canada; Trombovein, Omega Pharmaceuticals Ltd, Montreal, Quebec, Canada; and Fibro-vein, STD Pharmaceutical, Hereford, England)	0.5–2/10	++	Yes	\$48.50 per 2-mL vial
Polidocanol, 0.5%–3% (Ethoxysklerol, Kreussler Pharma, Weisbaden, Germany; and Sclerovein, Resinag AG, Zurich, Switzerland)	1–2/15–20	+	No	
Alcohols				
Ethanol 99.5%	0.5–1/4	++++	Yes	\$162 per gallon
Phenol 3%	3/36	+	Yes	\$30–40 per 50-mL vial
Sugars				
Hypertonic (50%) dextrose solution	Limited data; has only been used in combination with other agents		Yes	\$0.97 per 50-mL vial

*Prices current as of December 2006.

vials. Sodium tetradecyl sulfate may be injected in intra- or paravariceal locations. Paravariceal injection is reported to be associated with an increased incidence of complications.¹ The 1% solution is recommended for treatment of small varices and the 3% solution for large varices. The recommended dose is 0.5 to 2 mL (preferably 1 mL) per injection, with a maximum of 10 mL per session.⁴

Polidocanol

Polidocanol is hydroxyl-polyethoxydodecan ($C_{30}H_{62}O_{10}$). It is a synthetic anionic detergent available as 0.5%, 1%, 2%, and 3% solutions. It has been used both for para- and intra-variceal injections of esophageal varices, mostly in Europe and Asia.^{1,5–7} The usual dose is 1 to 2 mL per injection, with a volume of 15 to 20 mL per session. Polidocanol is not approved for use in the United States and is subject to confiscation if independently imported.⁸

Sodium morrhuate

Sodium morrhuate is a mixture of the sodium salts of the saturated and unsaturated fatty acids of cod liver oil. It is available as a pale yellow, granular powder, with a fishy

odor, which is soluble in water or alcohol. It is overlaid with filtered nitrogen to prevent discoloration to a darker color, which occurs on exposure to oxygen. Each milliliter contains 50 mg sodium morrhuate, 2% benzyl alcohol, and water adjusted to a pH of approximately 9.5 with sodium hydroxide. It is generally used as a 5% solution for intra- and paravariceal injection. It is supplied in 30-mL vials of 50 mg/mL. The solution for injection should be clear and should not be used if it is not clear. The solution may also have solid particles on standing, which dissolve on warming. It should not be used if such particles do not dissolve completely on warming. The recommended dose is 0.5 to 5 mL per injection, depending on the size of the varix, up to a maximum of 15 mL per session.^{1,4}

Ethanolamine oleate

Ethanolamine oleate ($C_{20}H_{41}NO_3$) is a combination of an organic base and oleic acid. It is available as a pale yellow solution or powder. It is used as a 5% solution and contains 50 mg ethanolamine oleate, with 2% benzyl alcohol per milliliter at a pH of 8 to 9. It is supplied in 2-mL

ampules. The recommended dose is 1.5 to 5 mL per injection, to a maximum of 20 mL per session.^{1,4}

Ethanol

Absolute alcohol (99.5% ethanol) (C₂H₅OH) has been used mostly in Asia for treatment of esophageal and gastric varices.¹ Intravariceal injection is preferred instead of paravariceal injection, which is associated with more complications.^{1,9,10} It is supplied in 1-gallon polyethylene or glass containers. An average of 0.5 to 1 mL is injected per varix to a maximum of 4 mL per session.^{9,10}

Pediatric dosing

Established pediatric doses are generally not available for any of the sclerosants. Many pediatric gastroenterologists use a quarter to a half of the adult dose in children <12 years of age, depending on size.

TECHNIQUE

To control bleeding from a varix, a sclerosant is dispensed with a sclerotherapy needle passed through the working channel of an endoscope. Sclerotherapy needles consist of an outer plastic sheath and an inner core channel attached to a needle at the tip. These needles are available from several vendors, in various needle calibers (21-25 gauge) and lengths.¹¹ The 25-gauge needle is typically used in children, whereas the 23-gauge needle, which provides higher flow rates, is typically used in adults. Sclerosants may be injected into intra- or paravariceal locations. The objective of intravariceal injection is to induce thrombosis and subsequent occlusion of the lumen of the varix. Paravariceal injection, however, occludes the varix by tamponade and induction of submucosal fibrosis of tissue around the varix.¹² Intravariceal injection requires less force but induces more temporary bleeding during the procedure.¹² There is no convincing evidence to suggest that one technique is better than the other. Pathologic and fluoroscopic studies suggest that up to 60% of injections thought to be intravariceal were actually paravariceal.¹

INDICATIONS

The conventional sclerosants, ethanolamine oleate, polidocanol, sodium tetradecyl sulfate, sodium morrhuate, and absolute alcohol, are indicated for acute endoscopic hemostasis and elective obliteration of bleeding esophageal varices. They have also been used alone or in combination with ligation or cyanoacrylate for the treatment of bleeding esophageal or junctional (esophagogastric) varices. The sclerosants are not indicated for primary prophylactic treatment of varices that have not bled.

Although, in the United States, sodium morrhuate and sodium tetradecyl sulfate are the most commonly used

sclerosants for treating bleeding esophageal varices, specific Food and Drug Administration approval for this purpose is available only for ethanolamine oleate. Sodium tetradecyl sulfate and sodium morrhuate are approved only for treatment of varicose veins in the lower extremities. Polidocanol and absolute alcohol are not approved for use as sclerosing agents in the United States.⁴

The use of sclerosants has also been reported for a number of nonvariceal applications, including treatment of bleeding peptic ulcers,¹³⁻²⁵ palliative treatment of esophageal cancer,²⁶⁻²⁸ treatment of Dieulafoy's lesions,^{29,30} and treatment of arteriovenous malformations in the GI tract.³¹ Except for the use in controlling bleeding from peptic ulcers, the reports of nonvariceal applications are few and isolated; there is no strong evidence that such therapies are safe or effective.

EASE OF USE

Sclerotherapy is a conceptually simple and straightforward procedure. The technical challenges relate primarily to difficult visualization, targeting of the injection needle, safe sedation, and airway management in the setting of active bleeding. There are no published data on the level of training necessary to achieve proficiency in injection sclerotherapy. The reader is referred to the ASGE guidelines on training.³²

The low-density, low-viscosity sclerosing solutions, such as alcohol and sodium tetradecyl sulfate, are generally easier to inject than the oily sclerosants, such as sodium morrhuate, ethanolamine, and polidocanol.^{1,12} Paravariceal injections require a little more force than intravariceal injections, and they induce less bleeding than intravariceal injections.¹²

EFFICACY AND COMPARATIVE STUDIES

Endoscopic sclerotherapy is successful in controlling active bleeding in more than 90% of patients and is effective in reducing the frequency and the severity of recurrent variceal bleeding.³³⁻³⁷ Several randomized prospective studies that compared 1 sclerosant with another in the treatment of bleeding esophageal varices have been reported. One randomized trial that compared sodium tetradecyl sulfate with sodium morrhuate found no difference between the 2 with regard to control of acute bleeding, obliteration of varices, transfusion requirements, and ulceration or stricture formation.³⁸ Another study found that tetradecyl sulfate obliterated varices in a shorter period than ethanolamine oleate did.³⁹ A third study found a higher rate of disappearance of red color signs and less transfusion requirements with ethanolamine than with sodium morrhuate.⁴⁰ Most studies found the sclerosants to be similarly efficacious,^{9,10,38,41} with some differences in cost, time to obliteration,^{39,41,42} or

number of treatment sessions.⁴⁰⁻⁴² Alcohol has consistently been shown to be associated with a significantly higher complication rate.^{7,42,43}

Gastric varices have been less successfully treated with sclerosing agents.³⁷ Many agents have been used for this purpose, including 1.5% sodium tetradecyl sulfate,⁴⁴ ethanolamine, and absolute alcohol.^{45,46} Initial hemostasis rates that ranged from 40% to 100% and recurrent bleeding rates that ranged from 36% to 87% have been reported.^{44,45,47-50} Esophagogastric junctional varices respond relatively better to sclerotherapy than isolated or gastric fundic varices.⁴⁵ One comparative nonrandomized study found cyanoacrylate to be much more efficacious than ethanolamine for the treatment of acute gastric variceal bleeding.⁵⁰ The combined use of ethanolamine and cyanoacrylate has been reported to produce rapid eradication of esophagogastric varices, with fewer number of injection sessions.^{51,52}

Several comparative studies that involved the use of sclerosants as treatment for acutely bleeding peptic ulcers are reported in the literature.¹³⁻²⁵ In 1 randomized prospective trial that involved 208 patients, absolute ethanol was found to be as safe and as effective as multipolar electrocoagulation and neodymium-yttrium aluminium garnet laser in the endoscopic therapy of acute bleeding peptic ulcers.¹⁴ Another study found injection with absolute ethanol to be as effective and safe as hemoclips in controlling bleeding from gastric ulcers.¹⁵ Similar results were also found in randomized prospective trials that compared absolute ethanol with ethanolamine oleate²⁰ and polidocanol with hemoclips.²⁴ Despite these studies that demonstrated relative efficacy and safety, multiple descriptive reports of ulceration and perforation from sclerosants, alcohol in particular, have constrained their use for nonvariceal applications.

Several studies and a meta-analysis compared endoscopic injection sclerotherapy with endoscopic variceal ligation for the treatment of bleeding esophageal varices.⁵³⁻⁵⁶ They generally demonstrated that ligation and sclerotherapy are equally effective in controlling variceal bleeding, but ligation is associated with a lower incidence of complications, fewer episodes of recurrent bleeding, and fewer sessions to obliterate varices.

SAFETY

Complications of sclerotherapy may occur with all the sclerosants in as many as 25% of patients.³³ Common problems include the following: chest pain, mucosal ulceration, bleeding, esophageal strictures and fistulas, pleural effusions, and sepsis. Uncommon occurrences include the following: esophageal or gastric dysmotility, mediastinitis, esophageal perforation, pneumonia, hypoxia, spontaneous bacterial peritonitis, portal vein thrombosis, and inadvertent vagotomy.⁵⁷ Squamous-cell carcinoma has been

reported as a possible late complication of esophageal variceal sclerotherapy.^{58,59}

Bacteremia has been reported in up to 50% of patients undergoing sclerotherapy.⁶⁰ Patients with cirrhosis and who are immunocompromised are at greater risk for bacteremia and should receive antibiotic prophylaxis before sclerotherapy. It is recommended that patients with mechanical prosthetic devices, a history of endocarditis, vascular grafts, surgical systemic-pulmonary shunts, or ascites be considered for antibiotic prophylaxis before sclerotherapy.³⁷

FINANCIAL CONSIDERATIONS

Costs for sclerosing agents and sclerotherapy needles may vary by institution. Representative costs for the available agents are listed in Table 1. Polidocanol is not available in the United States, but Internet-based pricing from a European manufacturer is \$55.20 per 50 g. Ethanol (95%) is approximately \$162 per gallon. Costs for 23- and 25-gauge sclerotherapy needles vary between approximately \$37 and \$57.

Endoscopic injection sclerotherapy may be billed by using the following Current Procedural Terminology (CPT)* codes, depending upon the procedure and the lesion being treated: 43243 (EGD with injection of varices), 43255 (EGD with control of bleeding, as for ulcer therapy), 43204 (esophagoscopy with injection sclerosis of esophageal varices), 43227 (esophagoscopy with control of bleeding) or 43201 (esophagoscopy with directed submucosal injection).

CONCLUSIONS

Endoscopic variceal ligation has replaced endoscopic sclerotherapy as the preferred treatment for hemostasis and obliteration of bleeding esophageal varices. Under certain circumstances, however, sclerotherapy may be combined with variceal ligation to control active bleeding in a patient with esophagogastric varices. In small children in whom band ligation is impossible because of size and in some parts of the world where economic constraints make band ligation unaffordable, endoscopic sclerotherapy may still be the treatment of choice for bleeding esophageal varices. None of the sclerosants has emerged as the ideal agent. A complication rate as high as 25% has been

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reported with the use of sclerosants to treat esophageal varices. Absolute alcohol, the cheapest of these agents, is associated with more frequent and severe complications.

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