Pharmacology of Sclerotherapy

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ABSTRACT

Sclerotherapy is the therapeutic use of sclerosants in the controlled destruction of undesired target tissues. Sclerosants have been used in vascular and nonvascular settings, both as primary and adjunctive therapy. Effective sclerotherapy requires a conceptual understanding of key questions about the process being treated, including the method of delivery, the presence of flow, and the required contact time to initiate sclerosis. However, beyond technique and delivery, practical and safe application of sclerotherapy requires an understanding of the uses, limitations, dosing, and side effects of sclerosants used during interventional radiology procedures. Agents discussed here include detergents and surfactants [ethanol, Sotradecol[®] (Bioniche Pharma, Pointe Claire, Quebec and Angiodynamics, Latham, NY), ethanolamine oleate], hypertonics (saline, glucose), and a review of several other types that are used less frequently.

KEYWORDS: Sclerotherapy, ethanol, Sotradecol[®], hypertonic solutions, ethanolamine oleate, sclerosants

Objectives: Upon completion of this article, the reader should be able to list the mechanisms of action, uses, limitations, and side effects of common sclerosants used during interventional radiology procedures.

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Sclerotherapy is the use of physical, chemical, and biological properties of an agent used to disrupt target tissue. This disruption allows the formation of sclerosed or “hardened” byproducts that following therapy have drastically changed or diminished functions. For instance, sclerotherapy results not only in occlusion of vascular structures similar to embolization, but also may limit recurrence, proliferation, or collateralization by permanently disrupting the endothelium of targeted vascular structures. Additionally, sclerotherapy’s biological effect extends beyond structures with an endothe-

lium; the epithelial lining of true cysts, capillary beds, and lymphatic structures, as well as bone cysts, have been targeted successfully.

For an agent to have potential as a sclerosant, it must have a physical, chemical, and/or biologic effect on the target tissue and induce a controlled inflammatory response. The inflammatory response is a result of cell damage with fibroblast proliferation that leads to sclerosis. In addition to fibrosis, agents may produce other effects such as thrombosis, extraction of proteins from lipids, denaturation of proteins, cell dehydration by

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osmosis, and physical obstruction by polymerization. The result of these processes is controlled disruption of the targeted tissues biologic function.

Sclerotherapy is on a continuum with embolotherapy, and several sclerosing agents are also embolic in nature. Strict sclerosants such as hypertonic solutions have no evidence of embolic effect and are actually washed out of the targeted tissues by high flow rates. Scleroembolic agents, such as alcohol of zein and absolute alcohol, obstruct flow via thrombosis and/or viscosity, key features shared with embolic agents such as Gelfoam[®] (Pfizer Pharmaceuticals, Inc., New York, NY). However, denaturation of proteins, denuded endothelium, and direct tissue damage beyond the vessel wall are features of a sclerosant, not an embolic agent. Conversely, agents that are considered embolic may also have sclerosant properties. For instance, cyanoacrylate, a polymer that is used to cause vascular obstruction, causes a moderate inflammatory response and may be better controlled than alcohol-based agents. This feature has been used in vascular lesions successfully, and in nonvascular lesions with moderate success.

Because a sclerosant depends on biologic, chemical, and physical processes to cause its intended effect, modeling of the target system becomes essential to understand the practical constraints of each agent. Mathematical models are beyond the scope of this article, but can be made practical by asking specific questions: What is the physical state of the target? Is there flow? Does the flow cause mixing? Is the target permeable? How quickly and how thoroughly does the sclerosant work on the target?

For a sclerosant to be effective, it must diffuse to its target tissue through a fluid medium and interact with the target tissue for a sufficient period to begin the process leading to sclerosis. Sclerosants are liquid, and diffusion from high to low concentrations will be on the order of centimeters per second (cm/s). Diffusion may be altered by turbulent flow such as that which occurs in a rapid flowing system, which may aid in mixing but carry away the agent. In contrast, slower laminar flow may allow traversal of the agent without mixing, making it entirely ineffective at the desired target. Either type of flow may lead to unintended embolization of liquid and even foam agents. The amount of flow together with permeability may also define a maximum agent concentration. This may be significant because it may alter the dose administered and target/nontarget distribution, such as in ethanol administration and potential patient intoxication. Finally, the kinetics of sclerosis must be matched with the above factors. For instance, even though osmotic dehydration begins immediately upon administration of hypertonic solutions, it is limited by flow in larger vessels, making it impractical in all but the smallest of vessels.

In this article, we will review the preparations, properties, uses, and side effects of the more common sclerotherapeutic agents used by interventional radiologists in the United States.

ETHANOL

Since its introduction as a sclerosant in canine renal models in 1980,³ ethanol has been the standard to which all other sclerosants have been compared. Its mechanism of action is a combination of cytotoxic damage induced by the denaturation and extraction of surface proteins, hypertonic dehydration of cells, and coagulation and thrombosis when blood products are present. All of these factors lead to fibrinoid necrosis.⁴⁻⁶ Ethanol's deep penetration into the vascular wall and lack of viscosity allows it to affect to most tissues, although its reactions are not tissue specific.⁷ The effect is dependent on ethanol concentration, time of exposure, and injection rate; rapid injection rates produce more endothelial damage and parenchymal necrosis with less thrombosis whereas slower rates produce more thrombosis, but less endothelial damage and necrosis.⁸ Occluding a vessel and allowing ethanol to dwell for 10 to 12 minutes can increase thrombosis and necrosis, although angiographic evidence of thrombosis is not required for infarction to occur.⁹ Ethanol has broad applications in both vascular and nonvascular interventions, although its use is limited by high complication rates and morbidity. Dosing should not exceed 1 mL/kg, as studies have demonstrated systemic blood alcohol concentrations of up to 0.07% at this dose.^{3,10}

Vascular applications of ethanol, initially reported by Sasaki¹ and by Yakes², include catheter or percutaneous injection of arteriovenous malformations (AVMs), venous malformations, varicoceles, and lymphatic malformations. In these settings, overall dosing is usually well below 1 mL/kg.³ Depending on the flow rate through the vessels and potential nontarget embolization, alcohol solution of zein has been used. Also known as Ethibloc[®] (Johnson and Johnson, Spreitenbach, Switzerland), it is alcohol in a viscous corn protein matrix, which allows for prolonged contact with tissue. However, it is not approved by the Food and Drug Administration (FDA) in the United States, and prolonged contact has led to frequent fistulization and adjacent tissue damage despite its decreased deep vascular permeation compared with 95% ethanol.¹⁰ The use of ethanol in neurologically sensitive areas has decreased with the advent of more easily controlled polymers such as *N*-butyl cyanoacrylate (NBCA) and Onyx[®] (Micro-Therapeutics, Inc., Irvine, CA).¹¹

Although the role of ethanol sclerotherapy in renal carcinoma and angiomyolipoma treatment is still being determined, research indicates that an average total dose of 15 mL is sufficient for intraarterial ethanol

renal ablation. Although currently used for palliative therapy and as an adjunct to nephrectomy for renal devascularization, sclerotherapy is being studied to determine possible uses as single therapy for definitive treatment.³

Intravariceal injection of 10 to 12 mL of 95% ethanol has traditionally been used to treat esophageal varices, although this technique has been superseded by new interventional and endoscopic techniques such as banding.^{3,12}

Limited evidence and research is available for the use of ethanol for hepatic and splenic embolization. Percutaneous injection of hepatic tumors with ethanol has been used successfully in the treatment of small tumors in patients with excellent hepatic reserve.³ Although still used in Europe, percutaneous ethanol injection has largely been supplanted by other techniques in the United States.

Ethanol has been used in neurolysis, but given its high solubility and lighter density than cerebral spinal fluid (CSF), phenol has largely replaced it for nerve blocks.¹³⁻¹⁵

Injection of ethanol is an effective treatment of renal cysts. Dosing volumes vary, and up to 50 mL or half the cyst volume, whichever volume is smaller, is typically used. The fluid within the cyst is usually removed with a drain and ethanol is injected into the cyst and allowed to dwell for at least 20 minutes to achieve sclerosis. Multiple sessions are often necessary and although efficacious, large cysts tend to respond less well. Complications beyond pain are rare, but may occur if the cyst is centrally located, increasing the chance of nearby vascular penetration or damage to the renal pelvis. Other cystic formations that have been treated with ethanol include hepatic cysts, hydatid cysts (type IV), aneurysmal bone cysts, and lymphoceles.^{16,17}

Parathyroid and thyroid tumor ablation has been performed effectively with ethanol, although effectiveness is limited by tumor size and adjacent tissue necrosis; neurologic symptoms have been reported.³

Complication rates and side effects of ethanol are extensive. Nontarget embolization, neuritis, and adjacent tissue necrosis is particularly common given ethanol's deep penetration, lack of viscosity, and lack of visibility for monitoring purposes. Yakes reported a 0.6% mortality rate in AVM treatments treated with ethanol.¹⁸ Tissues that are particularly sensitive to ethanol include neural tissue, mucosa, and epithelial cells. Alcohol intoxication is unlikely to be life-threatening if dosing is kept below 1 mL/kg. In neural tissue, ethanol is particularly effective at extracting surface protein and rising through CSF due to its lower density. Cases of nerve damage and Wallerian degeneration following ethanol injection have been reported. Neural damage is dependent on the proximity to tissue, volume of ethanol used, and concentration.¹⁹ There is also evidence of

dose-dependent acute pulmonary hypertension, and vasospasm has been reported during intravascular ethanol use¹¹; skin necrosis and fistulization have also been reported.³

End-organ embolization produces postembolization syndrome including nausea, vomiting, pain, and fever for up to 5 days. Some researchers have reported abscess formation and recommend the routine use of prophylactic antibiotics.

Complications following cyst treatment are generally more benign, and include transient hematuria (renal cysts) and rarely extravasation. Penetration of fluid-producing tissue occurs in 3 to 5 minutes, whereas capsule penetration occurs in 4 to 12 hours. Intoxication is the most common side effect given the higher volumes approaching 1 mL/kg used in these applications.¹⁷

There is also research indicating elevated serum prothrombin time (PT) and D-dimer, and decreased platelets and fibrinogen in a dose-response fashion when sclerosants are used. These changes are particularly noted when ethanol and Sotradecol[®] are used. Whether these statistically significant findings are clinically important remain to be determined.²⁰

SOTRADECOL[®]

Sotradecol[®] (sodium tetradecyl sulfate; STS) (Bioniche Pharma, Pointe Claire, Quebec and AngioDynamics, Latham, NY) is an anionic surfactant used as an intravascular sclerosing agent. It is the only detergent sclerosant approved by the FDA,²¹ and is approved specifically for superficial varicosities. There have also been reports of STS administration in the treatment of varicoceles, vascular malformations of the extremities, upper gastrointestinal bleeding, variceal bleeding, hemorrhagic tumors, gallbladder ablation, lymphoceles, and percutaneous ablation of oral lesions of Kaposi sarcoma and ganglion cysts.^{21,23}

Animal models have demonstrated efficacy of STS in the treatment of gonadal veins, gallbladders, and renal arteries.²⁴⁻²⁸ Sclerosis of canine renal arteries allows direct comparison to ethanol sclerosis. Use in the gallbladder is consistent with other sclerosing agents as an alternative to cholecystectomy. The only reported complications in the dog renal model relate to reflux of STS into nontarget vessels; significantly, the use of STS did not demonstrate pathologic pulmonary sequelae such as pulmonary hypertension that may be seen following the administration of ethanol. Organized thrombus, denudation of endothelium, inflammatory response, and permanent luminal occlusion and sclerosis was noted in the STS experiments. These properties are similar to those reported for ethanol, although the exact mechanism of action is not fully understood.

Commercially available STS preparations include 1% or 3% solutions, with common total dosing of 0.5

mL to 2 mL (although use of up to 6 mL during a single session has been reported).²⁹ Sodium tetradecyl sulfate may be used as a stand-alone agent, as in direct percutaneous injection into superficial varicosities and large hemangiomas where there is minimal blood flow and maximum contact surface allowing for prolonged exposure.³⁰ However, this approach often requires multiple sessions. Catheter-directed foam sclerotherapy has been used effectively in single-session varicocele treatments. Foam preparation of 1 mL 3% STS mixed with 4 mL of air is believed to improve endothelial surface contact, and slows or stops flow allowing for extended periods of contact. The use of foam also allows use of lower doses of STS that may reduce complications. In applications with faster blood flow or decreasing volume to surface ratio (e.g., gallbladder), STS is typically used in combination with a temporary embolic agent (e.g., Gelfoam[®]), permanent embolic agent (e.g., polyvinyl alcohol [PVA], coils), and/or in combination with other sclerosants (e.g., 70% alcohol).

Gandini et al reported a retrospective evaluation of 244 men with grade II/III varicoceles, who presented with infertility (59/244) or other symptoms (e.g., pain) and who were treated with STS sclerotherapy.³¹ These individuals demonstrated a statistically significant increase in sperm counts, motility, and morphology following single-session foam sclerotherapy in an outpatient setting. Although long-term follow-up was not available, retreatment at 8 weeks was rarely needed (8/244). These findings represent an improvement over stand-alone coil embolization in which there are early and late recurrences due to clot lysis or coil erosion through the vein.³¹ Gandini and colleagues have also found similar benefits in female populations.³²

O'Donovan et al reported on 21 patients (49 procedures) with AVM, hemangioma, or venous malformation of the extremities who underwent treatment with 1- to 5-mL liquid of 3% Sotradecol[®]. In this study, 86% of the patients had decreased symptoms such as pain and swelling, although they frequently required repeat treatment and surgical excision.³⁰ Other studies have duplicated these results.³³

Gomes reported on the use of STS alone or in combination therapy (i.e., PVA and/or microfibrillar collagen) in the treatment of vascular malformations of the extremities. Eleven of 12 patients (91%) with percutaneously treated hemangiomas were symptom free for up to 3 years. Patients with high-flow malformations treated via a transcatheter approach reported an average of 2.4 years of relief of symptoms; treatment of venous malformations resulted in 3 symptom-free years.²⁹

Safe and effective definitive treatment or presurgical reduction of superficial malformations is feasible. Compared with the use of ethanol, STS is thought to be safer, although direct safety comparison studies are not

available. Several articles have reported consistently successful embolization of variceal bleeding, tumor bleeding, and upper gastrointestinal (GI) bleeding with Gelfoam[®] pledgets soaked with Sotradecol[®].³⁴ However, there are case reports of undesirable complications such as pulmonary and cerebral embolization and large intraabdominal hematomas as a result of this form of Gelfoam[®] embolization.³⁵ Published results are variable due to differences between angiographic success and durable clinical success.³⁶ The development of treatment for portal venous hypertension such as transjugular intrahepatic portosystemic shunting (TIPS), the advent of improved and wider variety of coils, the use of other potentially safer sclerosing agents, and advanced endoscopic techniques has made the use of STS for these indications much less common.

Animal models and preliminary human data have demonstrated relatively safe and effective combination ethanol/STS cystic duct and gallbladder sclerotherapy.³⁷⁻³⁹ However, the requirement of multiple treatments, associated costs, and availability of alternative, highly effective laparoscopic surgical treatments have made gallbladder sclerotherapy economically less desirable.⁴⁰

Numerous reviews and papers discuss the effective use of STS on superficial varicosities.⁴¹ However, because there is a broad set of available sclerosants such as ethanol, sodium morrhuate, and hypertonics, some of which are less expensive and others with better side-effect profiles, STS represents an alternative use often based on operator preference.^{21,42,43}

The use of STS in the treatment of lymphoceles, a postsurgical condition often treated with ethanol, has been reported effective in a single case report.⁴⁴

Complications directly related to STS tend to be at the site of administration; extravasation at or near the site of injection during percutaneous treatments has been widely reported.²¹ Varicocele treatment can lead to tissue damage near the site of extravasation due to venous injury. Scrotal swelling and pain also occur in a small number of patients, despite pretreatment with antiinflammatory medications and antibiotics. The swelling, however, is typically well controlled with additional antiinflammatory medication. Other potential complications include continued hemorrhage or recurrent hemorrhage in patients with upper GI bleeding, and pain. Rare transient focal neurologic symptoms such as visual disturbances and headaches may be observed with other sclerotherapy agents, and may be related to therapy delivery rather than the agent itself.²¹

There is minimal evidence of coagulation disturbances following the use of sclerosants such as ethanol and STS, including statistically significant prolonged PT, decreased platelets in a dose-dependent manner, a drop in fibrinogen, and increase in patients with positive D-dimer. In one study, most patients with

such disturbances were treated with a combination of ethanol and STS; only two patients were treated with STS alone, which was reported at a dose of 0.5 mL/kg.⁴⁵

No pulmonary complications similar to ethanol have been reported with the use of STS. Additionally, rates of anaphylaxis are not out of proportion to those seen with other sclerosants.

ETHANOLAMINE

Ethanolamine oleate (EO, Ethamolin[®]; QOL Medical, LLC, Kirkland, WA) is a sclerosing agent prepared in 50 mg per mL of aqueous solution; it is available from its manufacturer in 2 mL ampules.⁴⁶ Standard dosing is usually one ampule per session. Early animal model studies suggest that ethanolamine completely inhibits coagulation at concentrations as low as 0.31%, and induces sclerosis via endothelial damage leading to fibrin-product deposition and thrombosis hours after exposure. Its excellent thrombosing effect adds to the efficacy of EO sclerosis. It is thought that the oleate component functions to induce a further inflammatory response, which extends beyond the vessel to surrounding tissues.⁴⁷

Despite FDA-approval, EO is not as frequently used in the United States because of its adverse side effects, including frequent perivascular infiltration⁴⁸ when used endoscopically.⁴⁹ However, it is the only FDA-approved sclerosant for rebleeding of esophageal varices (although it is not indicated for prophylactic variceal treatment).¹² Additional uses include treatment of gastric varices, percutaneous transhepatic portal embolization,⁵⁰ and AVMs.^{51,52} Kyosue et al have used 5% ethanolamine oleate with excellent technical results as an alternative to NBCA in selected patients with gastric varices by stepwise injection in intervals of 3 to 15 minutes within selected segments of target vessels.⁴⁸

The advantage of EO over ethanol is its less-severe and less-frequent side effects. Ethanolamine does not invade the vascular wall as deeply as ethanol, reducing the potential risk to adjacent soft tissue structures and nerves.⁵³ This advantage is lost, however, when delivery is extravascular.⁵² The most important side effect seen with extravascular administration is hemolysis with renal failure that requires prophylactic administration of albumin and treatment with haptoglobin. Exacerbation of heart failure, pleural effusions, and right-sided heart failure has also been reported, likely related to the broad intravascular distribution of EO.⁵³

HYPEROSMOTIC/HYPERTONIC AGENTS

Hyperosmotic agents cause dehydration of target cells, inducing cell damage and death. Osmosis is a force causing the movement of a solvent (i.e., water) across a

semipermeable membrane (i.e., cell membrane) not permeable to the solute (i.e., hypertonic saline, glucose), and its effect is directly related to the concentration gradient across the membrane. Ionic solutions such as saline maximize the number of solute particles by splitting into their ionic constituents (the Van't Hoff effect), whereas organic molecules such as glucose and mannitol require relatively higher concentrations. The effect is strictly based on concentration gradients and the nature of the agent is important in terms of patient safety rather than osmotic effect.

Osmotic force is present as soon as the gradient is established, but because the desired effect is dehydration, time is required for the movement of water across the membrane. The greater the concentration differential, the greater the force, and presumably the faster the flow of water across the membrane leads to quicker dehydration of the target cell.

Because osmosis is related to concentrations and cannot be specifically targeted, its use is limited by effects on nontarget cells that will also dehydrate (e.g., red blood cells in vasculature, surrounding parenchymal or stromal cells), the presence and concentration of nearby fluid, and the presence of physical barriers that are impermeable to water. An absent barrier leads to a series of gradients, and water that flows into the hypertonic solution is replaced by fluid in the interstitium and other, more distant cells. Additionally, diffusion of the hyperosmotic agent and flow may dilute the agent and even carry it away from the intended target.

Hyperosmotic stress on cells can have a variety of outcomes. Hypertonic saline results in small vessel sclerosis in animal models, scolical effect with cyst resolution in humans with echinococcosis,⁵⁵ and anecdotal evidence of small vessel sclerosis in humans.⁵⁶ The physiologic process responsible for these effects, apoptosis versus necrosis versus fibrosis, has not been fully elucidated. Interestingly, hypertonic (7%) saline solutions are actually beneficial in trauma patients, reducing edema and areas of cerebral necrotic tissue, whereas animal models have demonstrated decreased levels of GI mucosal cell apoptosis.⁵⁷ Hypertonic glucose has a body of evidence from the peritoneal dialysis literature demonstrating a complex effect on peritoneal cells. In this patient population, primary and secondary necrosis, apoptosis, and fibrosis have all been seen with chronic exposure to hypertonic glucose solutions. Evaluation of tissue samples also demonstrated that peritoneal tissue produces an increased number of sodium-potassium pumps, and tend to recruit more fibroblasts leading to encapsulating fibrosis. Additionally, animal models demonstrate increased levels of apoptosis in endothelial cells exposed to hypertonic mannitol. This suggests that although different hyperosmotic solutions produce a similar physical response of dehydration, the actual

physiology leading to cell death may be different. Further research is needed to characterize these effects.⁵⁸⁻⁶⁰

Hypertonic saline is not an FDA-approved sclerosant, but is consistently used in the United States. It is available in 23.4% and 11.7% concentrations; it is ubiquitous, inexpensive, easy to store, and concentrations can be easily adjusted by dilution.

An extensive body of research in the dermatologic literature has demonstrated the safe and effective use of hypertonic saline for small, superficial venous structures such as telangiectasias, varicose veins, and reticular veins.⁵⁶ Use of special lighting, recumbent position of the patient, and repeated small injections have been used by practitioners to improve results and reduce potential side effects. Administration is from large central vessel to smaller peripheral vessels, and consistent postprocedural compression improves results. A key consideration is blood flow through a target vessel because mixing will reduce the effectiveness and control of the agent to the target tissues by blood flow movement. Therefore, there are significant limits to the vessel size that can be effectively targeted with hypertonic saline.^{21,42}

Hypertonic saline has also been used as a sclerosant in patients with echinococcosis and thereafter to sclerose the abscess cavity. This represents one of many approaches that include use of antiparasitics (i.e., albendazole) and other sclerosing agents (i.e., dehydrated ethanol), or a combination thereof.^{55,61}

The safety profile of hypertonic saline is excellent at the low volumes used in interventional radiology. There is no expected anaphylactic or allergic reaction when preservative-free preparations are used. The most common complication is residual blood pooling in treated vessels, which can be easily aspirated at follow up. Nearby tissue necrosis including skin ulceration secondary to extravasation from the target vessel is the most concerning complication. Presumably, this is also a concern with sclerosis of nonvascular targets such as cysts, although no literature that addresses this is available. Additionally, pain occurs during injection and skin discoloration may occur due to extravasated red blood cells. When extravasation occurs, massaging the injected tissue and removing any excess solution may achieve rapid diffusion of the hypertonic saline. Using lower concentrations of hypertonic saline may mitigate pain and skin discoloration.^{62,63}

Hypertonic glucose (in concentrations of up to 70%) has been used as a sclerosant. Hypertonic glucose has been used in treatment of varicose veins, varicoceles, gastric varices, hydatid cysts,^{64,65} AVMs, and lymphatic malformations. Although generally not very effective as a single agent, evidence suggests that it may prime other agents and increase their effectiveness. The safety profile of hypertonic glucose is excellent and no complications are generally expected.

N-Butyl Cyanoacrylate

N-butyl cyanoacrylate (NBCA) is a polymeric embolic agent used commonly to treat vascular malformations. Its advantages include relatively precise control over placement and control of the rate of polymerization. The polymeric reaction is exothermic with evidence of giant cell reaction and fibrosis likely contributing to its effectiveness.^{11,49} These features have been used in sclerotherapy of gastric varices,^{48,66,67} as well as in non-vascular systems such as aneurysmal bone cysts⁸ and renal cysts.^{68,69} Its limiting factor as a sclerosant is its embolic effect, which may lead to nontarget embolization and prevent complete sclerosis of the targeted structure. Additionally, use of NBCA requires replacement of the delivery catheter after each administration, as it may occlude the catheter or cause adhesion of the catheter to native tissues.

Boiling Contrast

First demonstrated as a sclerosing agent by Amplatz at the University of Minnesota in 1981, boiling contrast to 100 degrees has been used effectively in the treatment of varicoceles.⁷⁰ Heated contrast is toxic to tissue, causes thermal damage, and is hyperosmotic. Its radiopacity allows close monitoring and rapid mixing with blood limits its site of action to target tissue only. Once cooled, the contrast is no longer toxic. Thrombosis is not immediate, occurring 1 to 5 days after administration. Boiling contrast has only been proven effective for varicoceles, but has failed in the treatment of AVMs. The most significant side effect is excessive pain.⁷¹

Sodium Morrhuate

Sodium morrhuate has been used as a varicose vein sclerosant since the 1940s in the United States and was initially used in 1933 for ablation of lymphatic malformations in Europe. Although FDA-approved, reports of intolerably high anaphylactic reactions and complications from extravasation (i.e., severe pain and skin necrosis) have limited its current use.^{12,21,71} Besides superficial varicose vein treatment, sodium morrhuate has been used as the active ingredient in Varikocid[®] (Kreussler, Wiesbaden, Germany) for treatment of varicoceles, although other agents are more commonly used today.⁷² A more recent application of sodium morrhuate has been as a 5% solution in Gelfoam[®] slurry for the treatment of pelvic congestion syndrome. As with Sotradecol[®], use of foam increases endothelial exposure to the agent and reduces the required dose, thereby limiting potential side effects.²¹

Sclerodex[®]

Sclerodex[®] (Omega Laboratories, Richmond, British Columbia, Canada) is a combination of hypertonic

Table 1 Comparison of Benefits and Risks of Commonly Used Sclerotherapeutic Agents

Agent	Benefits	Risks
Ethanol	Inexpensive Highly effective Broad applications in vascular and nonvascular interventions	Nontargeted embolization Adjacent tissue damage High neural tissue sensitivity High mucosal tissue sensitivity Pain Alcohol intoxication Acute pulmonary hypertension
Sotradecol®	Effective at low concentrations Less cytotoxic than ethanol Intravascular injection painless	Expensive Pain and possible skin necrosis with extravasation
Ethamolin®	Decreased penetration of vessel walls Less cytotoxic than ethanol	Renal failure Exacerbation of heart failure
Hypertonic saline	Inexpensive Concentrations easily adjusted Lack of allergenicity if use preservative-free preparations	Failure of therapy Tissue necrosis and ulcerations with extravasation Pain

glucose and saline. It has mild sclerosing potential and reduced side effects when compared with higher concentrations of saline or glucose. Although approved in Europe, its use is not sanctioned and is actively discouraged by the FDA.²¹

Polidocanol

Polidocanol is a non-FDA approved sclerosing agent used in Europe for the treatment of varicoceles and varices. Similar to sodium morrhuate and hypertonics, the most significant side effect is soft tissue necrosis due to extravasation.^{10,21}

Bleomycin

Originally developed as an antibiotic and eventually used a chemotherapeutic agent due to its effect on DNA, bleomycin has been noted to cause fibrosis. This agent has been used for pleurodesis in the treatment of malignant pleural effusions. Bleomycin has had limited success in the treatment of pediatric lymphatic malformations, but has a good safety profile.¹⁰

OK 432

Also known as Picibanil® (Chugai Pharmaceutical Co., Tokyo, Japan), OK 432 is a biologic product created from the incubation of group A *streptococcus* with penicillin. Unlike other sclerotherapy agents, this agent is a natural killer cell activator and has been effectively used in the treatment of peritoneal carcinomatosis and pediatric lymphatic malformations by direct percutaneous injection.¹⁰

OTHER AGENTS USED IN CYST ABLATION

Many agents have been used in the treatment of cysts, particularly renal cysts and hydatid cysts, with satisfactory results. Among these agents are doxycycline, tetracycline, povidone-iodine (Betadine), acetic acid, phenol, Pantopaque, bismuth, hypertonic saline, albendazole infusion, hypertonic glucose, and honey.^{17,55,73} None of these agents has consistently demonstrated greater efficacy or a better safety profile than ethanol.¹⁷

CONCLUSION

Sclerosants are used in both vascular and nonvascular interventional procedures. It is important to understand concepts such as the mechanisms of action; methods of delivery, flow, and required contact times; in addition to their uses, limitations, and side effects to ensure safe use of these agents in clinical practice. The risks and benefits of the more common agents discussed in this article are summarized in Table 1.

REFERENCES

1. Sasaki M, Tadokoro S, Kimura S, Mori M, Kosuda S, Tachibana M. Two cases of renal arteriovenous fistula treated by transcatheter embolization with absolute ethanol. *Hinyokika Kiyo* 1984;30(3):295–298
2. Yakes WF, Pevsner P, Reed M, Donohue HJ, Ghaed N. Serial embolizations of an extremity arteriovenous malformation with alcohol via direct percutaneous puncture. *AJR Am J Roentgenol* 1986;146(5):1038–1040
3. Becker GH, Holden RW, Heun YY, Klatte EC. Ablation with absolute alcohol. In: Castaneda-Zuniga WR, Tadavarthi SM, eds. *Interventional Radiology*. Baltimore: Williams and Wilkins; 1992:135–152

4. Ellman BA, Green CE, Eigenbrodt E, Garriott JC, Curry TS. Renal infarction with absolute ethanol. *Invest Radiol* 1980;15(4):318-322
5. Do YS, Yakes WF, Shin SW, et al. Ethanol embolization of arteriovenous malformations: interim results. *Radiology* 2005;235(2):674-682
6. Mourao GS, Hodes JE, Gobin YP, Casasco A, Aymard A, Merland JJ. Curative treatment of scalp arteriovenous fistulas by direct puncture and embolization with absolute alcohol. Report of three cases. *J Neurosurg* 1991;75(4):634-637
7. Hyodoh H, Hori M, Akiba H, Tamakawa M, Hyodoh K, Hareyama M. Peripheral vascular malformations: imaging, treatment approaches, and therapeutic issues. *Radiographics* 2005;25(Suppl 1):S159-S171
8. Ellman BA, Parkhill BJ, Marcus PB, Curry TS, Peters PC. Renal ablation with absolute ethanol. Mechanism of action. *Invest Radiol* 1984;19(5):416-423
9. Rabe FE, Yune HY, Richmond BD, Klatte EC. Renal tumor infarction with absolute ethanol. *AJR Am J Roentgenol* 1982;139:343-345
10. Dubois J, Garel L, Gordon Culham JA. Pediatric interventional angiography. In: Baum S, Pentecost MJ, eds. *Abrams' Angiography Interventional Radiology*. 2nd ed. Philadelphia: Lippincott Williams and Wilkins; 2006:1047-1068
11. Katz JM, Gobin YP, Riina HA. Techniques and devices in interventional neuroradiology. In: Hurst RW, Rosenwasser RH, eds. *Interventional Neuroradiology*. New York: Informa; 2008:161-182
12. American Society of Gastroenterology. Technology Status Evaluation Report: Sclerosing agents for use in GI endoscopy. *Gastrointest Endosc* 2007;66(1):1-6
13. Moller JE, Helweg-Larsen J, Jacobsen E. Histopathological lesions in the sciatic nerve of the rat following perineural application of phenol and alcohol solutions. *Dan Med Bull* 1969;16(4):116-119
14. Rumsby MG, Finean JB. The action of organic solvents on the myelin sheath of peripheral nerve tissue. 3. Chlorinated hydrocarbons. *J Neurochem* 1966;13(12):1513-1515
15. Politis MJ, Schaumburg HH, Spencer PS. Neurotoxicity of selected chemicals. In: Spencer PS, Schaumburg HH, eds. *Experimental and chemical neurotoxicity*. Baltimore: Williams and Wilkins; 1980:613-630
16. Simonetti G, Profili S, Sergiacomi GL, Meloni GB, Orlacchio A. Percutaneous treatment of hepatic cysts by aspiration and sclerotherapy. *Cardiovasc Intervent Radiol* 1993;16(2):81-84
17. Darcy M. Renal cysts and urinomas. In: Baum S, Pentecost MJ, eds. *Abrams' Angiography Interventional Radiology*. 2nd ed. Philadelphia: Lippincott Williams and Wilkins; 2006:764-776
18. Yakes WS, Parker SH. Diagnosis and management of vascular anomalies. In: Castaneda-Zuniga WR, Tadavarthy SM, eds. *Interventional Radiology*. Baltimore: Williams and Wilkins; 1992:152-189
19. Phan P, Burton AW. Interventional pain procedures for cancer pain. In: Baum S, Pentecost MJ, eds. *Abrams' Angiography Interventional Radiology*. 2nd ed. Philadelphia: Lippincott Williams and Wilkins; 2006:31-55
20. Mason KP, Neufeld EJ, Karian VE, Zurakowski D, Koka BV, Burrows PE. Coagulation abnormalities in pediatric and adult patients after sclerotherapy or embolization of vascular anomalies. *AJR Am J Roentgenol* 2001;177(6):1359-1363
21. Dietzek CL. Sclerotherapy: introduction to solutions and techniques. *Perspect Vasc Surg Endovasc Ther* 2007;19(3):317-324
22. Ramírez-Amador V, Esquivel-Pedraza L, Lozada-Nur F, et al. Intralesional vinblastine vs. 3% sodium tetradecyl sulfate for the treatment of oral Kaposi's sarcoma. A double blind, randomized clinical trial. *Oral Oncol* 2002;38(5):460-467
23. Ajekigbe L, Stothard J. The effectiveness of sodium tetradecyl sodium in the treatment of wrist ganglia. *Can J Plast Surg* 2006 Spring;14(1):28-30
24. Cho KJ, Brady TM, Anver MR. Renal artery occlusion and infarction with Sotradecol. *Invest Radiol* 1983;18(1):68-73
25. Becker GJ, Kopecky KK. Can the newer interventional procedures replace cholecystectomy for cholecystolithiasis? The potential role of percutaneous cystic duct ablation. *Radiology* 1988;167(1):275-279
26. Kinnison ML, Kadir S, Strandberg JD, Anderson JH, White RI Jr. Percutaneous spermatic vein occlusion: evaluation of sclerosing agents in experimental animals. *Radiology* 1986;161(2):299-301
27. Girard MJ, Saini S, Mueller PR, et al. Percutaneous chemical gallbladder sclerosis after laser-induced cystic duct obliteration: results in an experimental model. *AJR Am J Roentgenol* 1992;159(5):997-999
28. Becker CD, Quenville NF, Burhenne HJ. Gallbladder ablation through radiologic intervention: an experimental alternative to cholecystectomy. *Radiology* 1989;171(1):235-240
29. Gomes AS. Embolization therapy of congenital arteriovenous malformations: use of alternate approaches. *Radiology* 1994;190(1):191-198
30. O'Donovan JC, Donaldson JS, Morello FP, Pensler JM, Vogelzang RL, Bauer B. Symptomatic hemangiomas and venous malformations in infants, children, and young adults: treatment with percutaneous injection of sodium tetradecyl sulfate. *AJR Am J Roentgenol* 1997;169(3):723-729
31. Gandini R, Konda D, Reale CA, et al. Male varicocele: transcatheter foam sclerotherapy with sodium tetradecyl sulfate—outcome in 244 patients. *Radiology* 2008;246(2):612-618
32. Gandini R, Chiocchi M, Konda D, Pampana E, Fabiano S, Simonetti G. Transcatheter foam sclerotherapy of symptomatic female varicocele with sodium-tetradecyl-sulfate foam. *Cardiovasc Intervent Radiol* 2008;31(4):778-784
33. Tan KT, Kirby J, Rajan DK, Hayeems E, Beecroft JR, Simons ME. Percutaneous sodium tetradecyl sulfate sclerotherapy for peripheral venous vascular malformations: a single-center experience. *J Vasc Interv Radiol* 2007;18(3):343-351
34. Pereiras R, Viamonte MJr, Russell E, LePage J, White P, Hutson D. New techniques for interruption of gastroesophageal venous blood flow. *Radiology* 1977;124(2):313-323
35. Ellman BA, Curry TS III, Glotzbach RE, Simpson PR. Systemic embolization as a complication of transhepatic venography. *Radiology* 1981;141(1):67-71
36. Feldman L, Greenfield AJ, Waltman AC, et al. Transcatheter vessel occlusion: angiographic results versus clinical success. *Radiology* 1983;147(1):1-5
37. Becker CD, Fache JS, Malone DE, Stoller JL, Burhenne HJ. Ablation of the cystic duct and gallbladder: clinical observations. *Radiology* 1990;176(3):687-690

38. Becker GJ, Kopecky KK. Can the newer interventional procedures replace cholecystectomy for cholecystolithiasis? The potential role of percutaneous cystic duct ablation. *Radiology* 1988;167(1):275-279
39. Girard MJ, Saini S, Mueller PR, et al. Percutaneous chemical gallbladder sclerosis after laser-induced cystic duct obliteration: results in an experimental model. *AJR Am J Roentgenol* 1992;159(5):997-999
40. Martin EC, Getrajdman GI. Does the gallbladder have a future? *Radiology* 1989;170(3 Pt 2):969-973
41. Bergan J, Pascarella L, Mekenas L. Venous disorders: treatment with sclerosant foam. *J Cardiovasc Surg (Torino)* 2006;47(1):9-18
42. Tisi PV, Beverley C, Rees A. Injection sclerotherapy for varicose veins. *Cochrane Database of Systematic Reviews* 2006, Issue 4. Art. No.: CD001732. DOI:10.1002/14651858.CD001732.pub2
43. Coleridge Smith P. Saphenous ablation: sclerosant or sclerofoam? *Semin Vasc Surg* 2005;18(1):19-24
44. Pope AJ, Ormiston MC, Bogod DG. Sclerotherapy in the treatment of recurrent lymphocele. *Postgrad Med J* 1982;58(683):573-574
45. Mason KP, Neufeld EJ, Karian VE, Zurakowski D, Koka BV, Burrows PE. Coagulation abnormalities in pediatric and adult patients after sclerotherapy or embolization of vascular anomalies. *AJR Am J Roentgenol* 2001;177(6):1359-1363
46. QOL Medical. Corporate Web site. Available at: www.ethamolin.net. Accessed January 10, 2010
47. Masaki M, Obara K, Suzuki S, et al. The destructive effects of sclerosant ethanolamine oleate on mammalian vessel endothelium. *Gastroenterol Jpn* 1990;25(2):230-235
48. Kiyosue H, Mori H, Matsumoto S, Yamada Y, Hori Y, Okino Y. Transcatheter obliteration of gastric varices: Part 2. Strategy and techniques based on hemodynamic features. *Radiographics* 2003;23(4):921-937; discussion 937
49. Coldwell DM. Invited Commentary. *Radiographics* 2003;23:937
50. Beppu T, Iwatsuki M, Okabe H, et al. A new approach to percutaneous transhepatic portal embolization using ethanolamine oleate iopamidol. *J Gastroenterol* 2010;45(2):211-217
51. Kaji N, Kurita M, Ozaki M, et al. Experience of sclerotherapy and emboloscclerotherapy using ethanolamine oleate for vascular malformations of the head and neck. *Scand J Plast Reconstr Surg Hand Surg* 2009;43(3):126-136
52. Hyodoh H, Akiba H, Hyodoh K, Ezoe K, Yotsuyanagi T, Hareyama M. Effects of blood flow control on clinical outcomes after ethanolamine oleate sclerotherapy for vascular malformations. *Jpn J Radiol* 2009;27(8):297-302
53. Hyodoh H, Hori M, Akiba H, Tamakawa M, Hyodoh K, Hareyama M. Peripheral vascular malformations: imaging, treatment approaches, and therapeutic issues. *Radiographics* 2005;25(Suppl 1):S159-S171
54. Kayama H, Inamori M, Togawa J, et al. Pleural effusions following endoscopic injection sclerotherapy for cirrhotic patients with esophageal varices. *Hepatogastroenterology* 2006;53(69):376-380
55. Kilicoglu B, Kismet K, Kilicoglu SS, et al. Effects of honey as a scolical agent on the hepatobiliary system. *World J Gastroenterol* 2008;14(13):2085-2088
56. Goldman MP. A comparison of sclerosing agents. Clinical and histologic effects of intravascular sodium morrhuate, ethanolamine oleate, hypertonic saline (11.7%), and sclerodex in the dorsal rabbit ear vein. *J Dermatol Surg Oncol* 1991;17(4):354-362
57. Lu YQ, Huang WD, Cai XJ, Gu LH, Mou HZ. Hypertonic saline resuscitation reduces apoptosis of intestinal mucosa in a rat model of hemorrhagic shock. *J Zhejiang Univ Sci B* 2008;9(11):879-884
58. Mactier RA. The spectrum of peritoneal fibrosing syndromes in peritoneal dialysis. *Adv Perit Dial* 2000;16:223-228
59. Soria M, Arrieta J, Ugarte I, Moina I, Guerra M, Escanero J. [Intracellular pH changes induced by sclerosing agents in peritoneal fibroblasts]. *Nefrologia* 2004;24(2):158-166
60. van Westrhenen R, Vlijm A, Hiralall JK, Krediet RT. Experimental study on long-term exposure to a biocompatible, hypertonic, pyruvate-buffered dialysis solution. *Perit Dial Int* 2008;28(Suppl 5):S43-S47
61. Akhan O, Gumus B, Akinci D, Karcaaltincaba M, Ozmen M. Diagnosis and percutaneous treatment of soft-tissue hydatid cysts. *Cardiovasc Intervent Radiol* 2007;30(3):419-425
62. Min T. Interventional radiology of venous insufficiency. In: Baum S, Pentecost MJ, eds. *Abrams' Angiography Interventional Radiology*. 2nd ed. Philadelphia: Lippincott Williams and Wilkins; 2006:1099-1109
63. Sadick NS. Hyperosmolar versus detergent sclerosing agents in sclerotherapy. Effect on distal vessel obliteration. *J Dermatol Surg Oncol* 1994;20(5):313-316
64. Aupetit JF, Ritz B, Ferrini M, Coppin M, Champsaur G. Images in cardiovascular medicine. Hydatid cyst of the interventricular septum. *Circulation* 1997;95(9):2325-2326
65. Salomon JL, Bourgeois A, Le Baleur A, Pillot P, Gillot C, Frileux C. [Product of choice for maintenance sclerosis: 66% glucose solution]. *Phlebologie* 1983;36(3):249-254
66. Consolo P, Luigiano C, Giacobbe G, Scaffidi MG, Pellicano R, Familiari L. Cyanoacrylate glue in the management of gastric varices. *Minerva Med* 2009;100(1):115-121
67. Kiyosue H, Mori H, Matsumoto S, Yamada Y, Hori Y, Okino Y. Transcatheter obliteration of gastric varices. Part 1. Anatomic classification. *Radiographics* 2003;23(4):911-920
68. Baysal T, Soylu A. Percutaneous treatment of simple renal cysts with n-butyl cyanoacrylate and iodized oil. *Diagn Interv Radiol* 2009;15(2):148-152
69. Kim SH, Moon MW, Lee HJ, Sim JS, Kim SH, Ahn C. Renal cyst ablation with n-butyl cyanoacrylate and iodized oil in symptomatic patients with autosomal dominant polycystic kidney disease: preliminary report. *Radiology* 2003;226(2):573-576
70. Cragg AH, Galliani CA, Rysavy JA, Castaneda-Zuniga WR, Amplatz K. Endovascular diathermic vessel occlusion. *Radiology* 1982;144(2):303-308
71. Herrera MA, Di Segni R, Kaye KW, et al. Embolization of the internal spermatic vein with mechanical devices for the treatment of varicocele. In: Castaneda-Zuniga WR, Tadarvarthy SM, eds. *Interventional Radiology*. Baltimore: Williams and Wilkins; 1992:100-110
72. VenBrux AC. Pelvic venous incompetence: pelvic congestion syndrome. In: Baum S, Pentecost MJ, eds. *Abrams' Angiography Interventional Radiology*. 2nd ed. Philadelphia: Lippincott Williams and Wilkins; 2006:830-836
73. Wible BC, Mitchell S. Doxycycline sclerotherapy of an intrasosseous femoral lymphatic malformation: case report and literature review. *J Vasc Interv Radiol* 2009;20(5):660-663