Cynthia K. Shortell, MD, **SECTION EDITOR**

An update on the currently available nonthermal ablative options in the management of superficial venous disease

Nathan W. Kugler, MD, *and* Kellie R. Brown, MD, *Milwaukee, Wisc*

ABSTRACT

Background: Chronic venous insufficiency affects millions of Americans with symptoms spanning a broad range. Saphenous incompetence resulting in chronic reflux is at the root of most disease and is amenable to surgical correction.

Methods: We conducted a systematic review of the literature on nonthermal ablative techniques using a MEDLINE (Ovid) search from January 2000 to August 2016. Only prospective studies and literature review articles in the English language were included for final analysis.

Results: A total of 358 unique articles were identified, with a total of 60 articles meeting the stated inclusion and exclusion criteria. Historically, nonthermal ablative techniques have not demonstrated clinical results on par with thermal ablative interventions. However, three newer nonthermal ablative techniques have become available for use in the United States. Review of the literature demonstrated significant improvements in nonthermal ablative results, with intermediate-term data suggesting improved durability.

Conclusions: Advances in nonthermal ablative techniques have led to a developing role and acceptance in the primary management of varicose veins and venous insufficiency, even in the setting of challenging cases. (J Vasc Surg: Venous and Lym Dis 2017;5:422-9.)

Chronic venous insufficiency, a common problem affecting nearly 30 million Americans, increases with age and can be manifested with debilitating symptoms including heaviness, aching, fatigue, and swelling.[1-5] Superficial venous insufficiency is often associated with saphenous venous incompetence, resulting in chronic reflux. These patients have long benefited from excision or ablation of the saphenous vein.[6] Initial management of chronic superficial venous disease is dependent on symptom severity. Symptom management using nonoperative techniques, including compression therapy and leg elevation, is ideal for patients who present early. The decision to proceed with intervention must encompass symptom severity, extent of disease, response to nonoperative management, and expectations of the patient. The Clinical, Etiology, Anatomy, and Pathophysiology (CEAP) classification system was developed to aid in stratification and clinical decision-making. Those individuals in whom venous reflux is persistently symptomatic are most likely to benefit from venous ablation.

Historically, saphenous vein ablation was accomplished by saphenofemoral junction (SFJ) ligation with partial or complete surgical vein excision. Randomized trials demonstrate a cost benefit, improved quality of life, and decreased ulcer recurrence rates with high ligation and vein stripping.[6,7] Open surgical management results in durable outcomes with 5-year treatment success rates near 75%.[7-9] Unfortunately, open surgical management results in significant early morbidity: ecchymosis in >60%, hematoma in 50% and tenderness in >25% of patients.[8] Less invasive techniques have decreased the morbidity associated with open surgery and have focused on thermal ablation of the vein through three primary mechanisms: radiofrequency, laser, and steam. Thermal ablative techniques rely on significant heat generation, resulting in desquamation of the venous endothelium, exposure of the underlying thrombogenic media, and transmural vein wall injury.[10] Whereas it is much less invasive than ligation and stripping, thermal ablation requires tumescent anesthetic administered along the length of the truncal vein for management of heat-associated pain. Randomized trials demonstrated durable venous closure rates (>85% at 4 years) with faster recovery, fewer complications, and improved quality of life after radiofrequency ablation (RFA) and endovenous laser ablation (EVLA) treatment compared with open surgical management.[8,11-14]

To address issues with thermal ablation, new nonthermal techniques have been developed that may provide some treatment advantages. Historically, nonthermal techniques have encompassed sclerotherapy, defined by injection of an irritant inducing endovenous inflammation, resulting in scar formation and

From the Department of Surgery, Division of Vascular Surgery, Medical College of Wisconsin.

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Correspondence: Kellie R. Brown, MD, Professor of Vascular Surgery and Radiology, Medical College of Wisconsin, 9200 W Wisconsin Ave, Milwaukee, WI 53226 (e-mail: krbrown@mcw.edu).

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lumen occlusion. A number of sclerotherapy agents (eg, sodium tetradecyl sulfate, polidocanol, hypertonic saline, glycerin) have been used in different preparations (eg, liquid, foam). Thus, we sought to evaluate the efficacy and potential benefits of nonthermal ablation through a review of the currently available literature.

METHODS

The MEDLINE (Ovid) database was queried for all prospective studies published in the English language between January 2000 and August 2016 employing the search terms ablation and saphenous vein to include the terms varicose and varicose veins. After identification of all articles that met the stated search criteria, duplicate articles were removed. The remaining articles were screened through review of abstracts. Articles with a focus on thermal ablation or surgical treatment were excluded from final review. Any articles with inclusion of nonthermal techniques were reviewed in their entirety.

RESULTS

MEDLINE search resulted in a total of 365 articles, with 358 remaining after removal of duplicates. Of the 358 unique articles identified, 210 were excluded because of analysis of thermal or surgical ablative techniques only. A total of 76 articles were excluded for a variety of reasons (unrelated, adjunctive techniques only, cardiac intervention, opinion articles), leaving a total of 74 nonthermal ablation articles for full-text review. On full-text review, an additional 14 articles were excluded (editorial articles, opinion pieces, expert consensus), leaving a total of 60 full-text articles for inclusion. The quality of the studies included within the review was variable; however, all studies included in the review were of at least level III evidence, with a large number of randomized trials constituting level II evidence.

DISCUSSION

A 2006 Cochrane review concluded that nonthermal techniques were inferior to open surgical management, with no significant differences among the commercially available sclerotherapy formulations at that time.[15] Since that review, three products have come to market in the United States: Varithena (BTG International Ltd, West Conshohocken, Pa), ClariVein (Vascular Insights LLC, Quincy, Mass), and VenaSeal (Sapheon, Inc, Morrisville, NC). All of these are Food and Drug Administration (FDA) approved for the treatment of symptomatic venous reflux disease diagnosed on ultrasound through permanent closure of the lower extremity superficial truncal veins. In addition, Varithena is FDA approved for the treatment of visible varicosities. Tables I and II list comparative statistics and product overviews.

Nonthermal techniques demonstrate favorable side effect profiles; minor pain, hyperpigmentation, and telangiectatic matting represent the majority of adverse reactions. Unfortunately, compared with EVLA, liquid sclerosant techniques have been technically less successful in achieving initial closure with increased rates of recanalization.[15] Endovenous foam therapy was developed to address the shortcomings of liquid sclerosants and was originally described in 1999 by Tessari, who demonstrated its utility for the management of both major and minor varicosities.[16] The Tessari method produces a dense endovenous foam by combination of air or carbon dioxide with liquid sclerosant, using a three-way stopcock and two sterile syringes. Foam expansion within the venous lumen ensures displacement of blood, optimizing the interaction of the sclerosant with the venous endothelium, ultimately maximizing the procoagulant effect of smaller dose sclerosants and resulting in a decreased risk of recanalization.[17]

Early research into endovenous foam sclerotherapy consisted of physician-prepared formulations, most commonly using polidocanol preparations. Polidocanol acts through activation of cellular calcium and nitric oxide pathways of the endothelial cells, resulting in cell death and subsequent cessation of nitric oxide production.[18] Despite consistency in the active sclerosant agent, the major issue with physician-prepared foam sclerosants is the variability in the final product as a result of differences in mixing technique or ratio of sclerosant/gas.[19,20]

Table I. Comparison of thermal and nonthermal ablative techniques

Technique	Early occlusion rate, %	1-year occlusion rate, %	2-year occlusion rate, %	3-year occlusion rate, %	4-year occlusion rate, %
RFA	90-100	85-98	85-96	68-92	89
EVLA	93-100	89-100	74-97	79-100	76-96
Endovenous foam	45-96	67-93	53-97	53-79	NA
ClariVein	87-99	88-97	96-97	NA	NA
VenaSeal	93-99	92-93	92	NA	NA

EVLA, Endovenous laser ablation; *NA*, not available; *RFA*, radiofrequency ablation.
van Eekeren RR, et al. Semin Vasc Surg 2014;27:118-36.
Morrison N, et al. J Vasc Surg 2015;61:985-94.
Almeida JI, et al. Phlebology 2015;30:397-404.

Table II. Overview of current Food and Drug Administration (FDA)-approved nonthermal ablative techniques

	Product description	Mechanism of action	Recent literature
Varithena	Endovenous foam technique that promotes venous endothelial damage through direct sclerosant interaction	1% Polidocanol	King JT, et al. Eur J Vasc Endovasc Surg 2015;50:784-93 Todd KL 3rd, et al. Phlebology 2014;29:608-18
ClariVein	Mechanochemical technique using a high-speed rotary wire system to promote mechanical disruption of the venous endothelium followed by liquid sclerosant to further endothelial damage	Mechanical disruption + any sclerosant	Witte ME, et al. Surg Technol Int 2015;26:219-25. van Eekeren RR, et al. J Vasc Surg Venous Lymphat Disord 2014;2:282-8
VenaSeal	Nonthermal, non-sclerosant-based technique that uses a proprietary adhesive	Cyanoacrylate	Proebstle TM, et al. J Vasc Surg Venous Lymphat Disord 2015;3:2-7 Morrison N, et al. J Vasc Surg 2015;61:985-94

Despite variability in the final product leading to differences in clinical efficacy, basic science and clinical trials have continually demonstrated systemic and local safety in all endovenous foam formulations even when they are administered by different methods.[18,21-31] Ultimately, the issue with physician-prepared formulations was poor durability. Whereas studies suggest that initial technical success rates approach 90% at 6 months, significant reductions exist at 1 year, with success rates between 72% and 74%.[26,32-34] Studies investigating the durability of physician-prepared formulations beyond 2 years demonstrate anatomic closure rates near 70%.[23,24,35,36] In addition to concerns with variability in physician-prepared formulations, debate exists as to the efficacy of different target concentrations (0.5%, 1%, and 3%).[37,38] Standardization of foam sclerosant therapy at different concentrations sought to improve clinical outcomes. Several major clinical trials have investigated the safety and efficacy of standardized endovenous foam formulations.

The Efficacy and Safety of Great Saphenous Vein Sclerotherapy Using Standardized Polidocanol Foam (ESAF) is an industry-sponsored multicenter randomized trial that evaluated patients who underwent standardized endovenous foam or liquid sclerosant therapy with a 3% polidocanol solution.[39] ESAF demonstrated superior closure rates 3 months after treatment with standardized foam preparations compared with liquid polidocanol.[39] Multiple other studies demonstrated significant advantages to endovenous foam treatment compared with liquid preparations, even in the setting of physician-prepared formulations.[39-42] In an attempt to stratify the clinical efficacy of different foam preparations, Polidocanol Endovenous Microfoam Versus Vehicle for the Treatment of Saphenofemoral Junction Incompetence (VANISH-2), an industry-sponsored, randomized, blinded trial, evaluated the safety and efficacy of polidocanol (0.5% and 1.0%) microfoam preparations against placebo.[43] Eight-week ultrasound evaluation demonstrated lack of SFJ reflux and vein occlusion in 86.2% of patients who received 1% polidocanol foam compared with 83.3% of those who received 0.5% polidocanol, with little dependence on original vein diameter.[43] Similarly, King et al conducted a follow-up industry-sponsored randomized study that evaluated differences in placebo and 0.125%, 0.5%, 1%, and 2% polidocanol foam among patients with similar CEAP class to VANISH-2.[44] King et al validated the findings of VANISH-2 as they demonstrated an 80.4% technical success rate with 1% polidocanol foam; however, this trial did fail to show significance over placebo among patients who received 0.5% polidocanol foam as only 58.8% demonstrated occlusion on duplex ultrasound.[44]

These major trials investigating standardized endovenous foam demonstrate significant overall adverse event (AE) rates: 60% in VANISH-2 and 78% in the study by King et al.[43,44] The majority of AEs in these trials were mild, consisting predominantly of extremity pain and tenderness, superficial thrombophlebitis, and injection site hematoma. ESAF demonstrated no serious AEs with no significant differences in minor events between treatment groups.[39] Interestingly, VANISH-2 demonstrated a significantly higher rate of deep venous thrombosis (DVT; 8.6% vs 0%) and common femoral vein thrombus (6.9% vs 3.35%) among individuals undergoing treatment with 1% polidocanol compared with those treated with 0.5% polidocanol foam.[43] However, King et al demonstrated no significant difference in the rate of DVT (2.0% vs 1.9%) in treatment with 1% polidocanol vs 0.5% polidocanol foam.

Whereas these major trials demonstrated the safety and efficacy of endovenous foam therapy, some have questioned the role of endovenous foam therapy compared with EVLA techniques. Foam sclerotherapy has been shown to be less expensive than EVLA; however, it has been suggested that some of that benefit is lost because of increased need for reintervention for definitive management.[36,45,46] Several randomized studies suggest long-term benefit to EVLA intervention; however, these trials are not focused on newer endovenous foam preparations.[32,36,47-49] Recent review articles suggest improved anatomic success after EVLA as measured by duplex ultrasound; however, overall clinical outcomes and safety are similar between EVLA and endovenous foam sclerotherapy.[46,50]

Given that the patient's symptoms guide the decision to intervene in the majority of cases, a focus on the patient's satisfaction and quality of life is essential. The majority of patient outcomes met or exceeded pretreatment expectations with quality of life improvements, as measured by Chronic Venous Insufficiency quality of life Questionnaire, in both the short- and long-term evaluation.[32,35,37,44,47,49,51-54] Studies demonstrated improved satisfaction of the patient with improved return to work after foam sclerotherapy compared with either EVLA or surgical intervention.[43,49,53,55] In addition, King et al demonstrated significant improvement in both varicose vein appearance (Independent Photography Review-Visible Varicose Veins and Patient Self-assessment of Visible Varicose Veins) and symptom scores (Varicose Vein Symptoms Questionnaire) with all polidocanol formulations, a finding shared by the VANISH-2 trial.[43,44]

In the United States, the Varithena system is a commercially available polidocanol foam product that addresses the concerns of physician-prepared formulations. Varithena offers consistent composition and bubble size that keeps its consistency longer than the typical physician-prepared products (Fig 1). The system consists of a 1% polidocanol foam delivered in a proprietary canister using low nitrogen concentrations that facilitate quick absorption. The procedure consists of ultrasound-guided percutaneous access of the refluxing truncal vein after detailed ultrasound mapping of the perforators. Perforators and any junctional connections with the deep system are manually compressed before foam injection, minimizing reflux of foam into the deep system. The leg is elevated to 45 degrees, and the foam is injected under ultrasound guidance. Extension of the foam into incompetent tributaries may occur, allowing treatment of these simultaneously with the truncal vein. Once injection is complete and spasm is noted on ultrasound, the leg is wrapped with the application of a foam pad over the injected veins to provide additional compression, and a 30 to 40 mm Hg compression stocking is traditionally placed, although several studies debate the utility of postprocedural compression.[56,57] Given the need for consistent pressure with injection under ultrasound guidance, this procedure is best performed with the aid of at least one assistant. In addition, as the procedure requires only local anesthesia at the site of venous access, this procedure is easily performed in an outpatient clinic setting.

Whereas the majority of the literature surrounding nonthermal ablative techniques centers on endovenous foam therapy, another nonthermal technique, ClariVein, was recently FDA approved. The ClariVein system involves both mechanical and chemical endothelial disruption (Fig 2). Mechanical disruption of the endothelium is achieved with a high-speed (2000-3500 rpm) rotary wire system. Mechanical damage is furthered by contact with liquid sclerosant, which is injected simultaneously with mechanical disruption. One of the benefits of the ClariVein system is that any liquid sclerosant may be used. Each of the different sclerosants promotes vein wall damage, thrombosis, and fibrosis through unique mechanisms of action. Early basic science studies demonstrated complete fibrotic sealing with extensive collagen production after treatment.[58] Although polidocanol continues to be one of the more common sclerosants used, a single multicenter blinded randomized

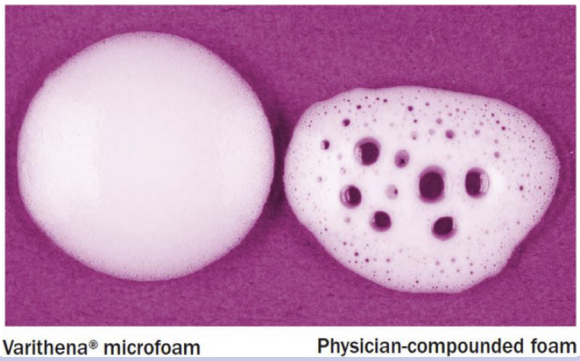

Fig 1. Varithena system highlights. The Varithena microfoam system provides significantly more consistent bubble size compared with physician-prepared microfoam compounds.

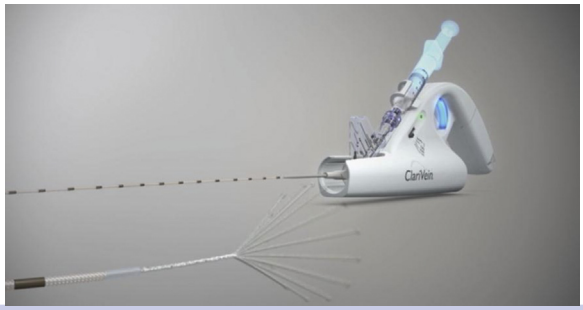

Fig 2. ClariVein system highlights. The ClariVein system uses a low-profile device that combines mechanical action with physician-infused sclerosant. The mechanochemical action of the ClariVein system maximizes endothelial disruption.

study questions the clinical efficacy, as measured by 6-week duplex ultrasound examination, of 1% polidocanol compared with 2% and 3% formulations.[59]

The ClariVein system was shown to have an initial technical success near 100%, with an 87% 6-week complete occlusion rate in an initial industry-sponsored trial.[60] Subsequent prospective trials confirmed excellent early technical success with occlusion rates of 94% to 99%.[61-64] Additional trials demonstrated significant improvements in periprocedural pain without compromise of venous occlusion rates compared with RFA.[64-66] A prospective observational study comparing laser ablation and ClariVein demonstrated less postoperative pain, faster recovery, and decreased time from work with use of the ClariVein system.[67] Although most studies done with ClariVein involve the great saphenous vein, Boersma et al demonstrated excellent technical success in the treatment of small saphenous vein insufficiency, with 1-year follow-up duplex ultrasound scans demonstrating a 94% closure rate.[68] Two-year results of the ClariVein system demonstrate a 96% success rate with retained improvement in patient-reported symptoms and quality of life.[69] There were no major complications, such as DVT, saphenous neuralgia, or skin necrosis, associated with the ClariVein system.[60,62,67] Because of the mechanical nature of the device, venous perforation is theoretically possible, although it has not been reported in any of the major trials. Rates of minor complications are comparable to those of other devices and include localized induration or ecchymosis at the puncture site (12%-36%), superficial phlebitis (3%-16%), localized hematoma (6%-9%), and hyperpigmentation (5%-9%).[60,62,67]

The procedure itself is easily performed in an outpatient clinic setting with only access site local anesthesia. Ultrasound-guided percutaneous access to the truncal vein is achieved, and a 4F sheath is placed. The catheter is advanced through the sheath with the wire positioned 2 cm distal to the SFJ using ultrasound guidance. The motor drive unit is connected and activated at the highest speed setting (3500 rpm) for 2 or 3 seconds to promote venospasm. The liquid sclerosant is then infused through a distal catheter port near the rotary wire as the catheter is withdrawn at a rate of 1 or 2 mm/s. Postprocedure compression is necessary, similar to EVLA and Varithena.

Finally, aside from foam sclerotherapy and mechanochemical ablation, the newest option in nonthermal ablative techniques is the VenaSeal system. VenaSeal is a non-sclerosant-based technique that uses a proprietary cyanoacrylate adhesive (Fig 3). It was FDA approved in February 2015 following multiple studies demonstrating its safety.[70-73] The VenaSeal system is different from previously described techniques as it does not rely on endothelial damage or scar formation for closure. Venous closure is achieved by use of a proprietary medical adhesive, essentially gluing the vein shut directly.

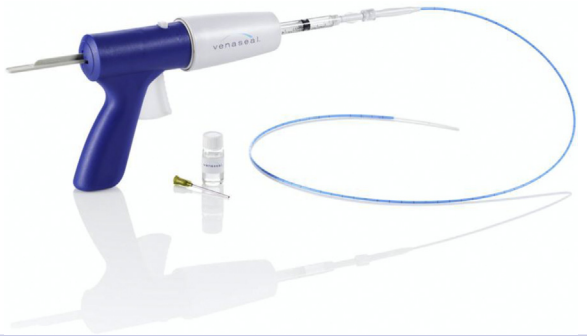

Fig 3. VenaSeal system highlights. The VenaSeal system uses a proprietary glue delivered through a catheter-based device.

VenaSeal Sapheon Closure System Pivotal Study (VeClose), an industry-sponsored randomized trial, investigated patients with CEAP C2-C4b disease and demonstrated the VenaSeal system to be noninferior to RFA at 3 months after treatment with closure rates of 99%.[72] Two-year follow-up data from an industry-sponsored nonrandomized prospective European trial looking at patients with CEAP C2-C4 disease demonstrated 92.0% closure rate at 24 months.[70] In addition, all patients demonstrated significant improvement in their Venous Clinical Severity Score, with the majority free from pain.[70] The VenaSeal system is associated with complications similar to those seen in other nonthermal ablative techniques, including hematoma, pain, phlebitis, and venous thrombosis. In the VeClose trial, 30% of patients experienced an AE, with 95% deemed mild to moderate in nature; phlebitis accounted for the majority of such events. Whereas the VeClose trial demonstrated no statistically significant difference in the AE rate (32% vs 24%; $P = .37$) compared with RFA, the rates of phlebitis (20% vs 14%; $P = .36$) and device-related complications (12% vs 6%; $P = .16$) were noted to be higher among those receiving treatment with VenaSeal.[72]

The procedure itself involves initial access of the truncal vein with advancement of the catheter to 5 cm distal to the SFJ using ultrasound guidance. The trigger mechanism delivers an initial 0.1 mL of the VenaSeal adhesive. The catheter is withdrawn 1 cm, followed by delivery of an additional 0.1 mL. The catheter is withdrawn an additional 3 cm, and the vein is manually compressed for 3 minutes. For the remaining length of the vein, 0.1 mL of VenaSeal adhesive is dispensed every 3 cm, followed by 30 seconds of compression after each dispersal. Similar to the other two available techniques, the VenaSeal system is easily used in an outpatient clinic setting as only access-site local anesthesia is required. Unlike with the other techniques, no postprocedure compression is required.

CONCLUSIONS

The initial data on nonthermal ablative techniques as highlighted in the 2006 Cochrane review demonstrated

the safety of these techniques but questioned their place as a primary technique for the management of superficial axial reflux.[15] Review of the recent literature on nonthermal ablative techniques demonstrates improvements in technique, technical success, and durability of results. The improvements in periprocedural pain and lack of need for tumescent anesthesia with nonthermal techniques provide a significant advantage. It is the authors' opinion that given advances in technology, nonthermal ablative techniques for the primary management of superficial venous insufficiency have acceptable success rates compared with thermal techniques and may be preferred in certain cases in which thermal techniques may have drawbacks, such as the below-knee saphenous vein or tortuous, superficial saphenous veins. However, long-term outcome data and head-to-head comparisons of the techniques are sparse in the literature. Whereas CEAP classifications help provide a basis for comparison regarding severity of disease, each trial has additional exclusion and inclusion criteria, which limits comparison. Finally, there are no good data, including no randomized trial, to allow comparison between nonthermal techniques.

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Writing the article: NK
Critical revision of the article: NK, KB
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