Journal of
Vascular Surgery
Venous and Lymphatic Disorders™

First human use of cyanoacrylate adhesive for treatment of saphenous vein incompetence

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Objective: **The primary objective of this study was to assess the feasibility of an endovenous cyanoacrylate (CA) adhesive implant, delivered with a catheter-based administration system engineered with a nonstick surface, for the treatment of incompetent great saphenous veins (GSVs). The primary safety end point was the rate of serious adverse events related to the procedure. The primary efficacy end point was vein occlusion during follow-up. Secondary end points included the rate of all adverse events and the change in Venous Clinical Severity Scores (VCSSs).**

Methods: **Thirty-eight incompetent GSVs in 38 symptomatic patients were treated by catheter deployment of CA under ultrasound guidance via a repetitive bolus injection algorithm. By protocol design, perivenous tumescent anesthesia and compression stockings were omitted. Duplex ultrasound imaging and clinical follow-up were performed immediately after the procedure, at 48 hours, and 1, 3, 6, and 12 months.**

Results: **The mean total volume of endovenous CA delivered was 1.3 ± 0.4 mL (range, 0.6-2.3 mL). Immediately after the procedure and at the 48-hour follow-up, the 38 patients (100%) demonstrated complete closure of the GSV. One complete and two partial recanalizations were observed during follow-up at 1, 3, and 6 months, respectively. Kaplan-Meier analysis yielded an occlusion rate of 92% at 12 months of follow-up. Side effects were generally mild and self-limited, most frequently, phlebitis in six patients (15.8%) requiring nonsteroidal anti-inflammatory drugs for an average of 5.7 days. Eight patients (21.1%) showed thread-like thrombus extensions into the common femoral vein of a mean length of 12.6 mm (range, 3.5-35 mm), which resolved spontaneously without anticoagulation. VCSS improved in all patients from a mean of 6.1 ± 2.7 at baseline to 1.5 ± 1.4 at 12 months ($P < .0001$). Edema improved in 34 legs (89%) at the 48-hour follow-up. At the 12-month follow-up, and without additional adjunctive treatment, 18 legs (50%) were free from visible varicosities and an additional eight legs (25%) showed limited varicosities.**

Conclusions: **The first human use of endovenous CA for closure of insufficient GSVs proved to be feasible, safe, and effective. Endovenous delivery of CA may prove to be an alternative for the correction of saphenous incompetence and may be used without tumescent anesthesia and medical compression stockings. (J Vasc Surg: Venous and Lym Dis 2013;1:174-80.)**

Endovenous laser and radiofrequency thermal ablation have proved to be safe and effective treatments for patients with signs and symptoms related to great saphenous vein (GSV) incompetence. Because of reduced convalescence and less pain and morbidity, the Society for Vascular Surgery and the American Venous Forum clinical practice guidelines have endorsed endovenous thermal ablation (EVTA) over traditional high ligation and stripping surgery.[1] Both EVTA techniques produce high venous occlusion rates with limited downtime[2-4]; however, both require the placement of perivenous tumescent anesthesia and, particularly with the use of endovenous laser, can cause vein wall perforations resulting in postoperative pain, bruising, paresthesia, and other complications.[5,6]

Ultrasound-guided foam sclerotherapy has garnered widespread popularity because of its low cost and high versatility. It is a chemical ablation technique useful for the treatment of the entire spectrum of CEAP C_{1-6} disease and can be performed using ultrasound guidance and low-cost disposables. However, patients usually need to return for reintervention to maintain vein closure, and postprocedural inflammation and staining are common occurrences. Visual disturbances upon injection of sclerosing agent occur in ~1.5% of patients,[7-9] and stroke related to paradoxic air embolism, although rare, can also occur.[10-12] In general, physicians recommend graduated compression stockings after all venous interventions to facilitate closure and mitigate side effects such as hematoma and edema.

A new, nonablative procedure using a proprietary formulation of cyanoacrylate (CA) adhesive delivered endovenously has been developed to improve upon some of the aforementioned limitations. CA is approved as an

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This study was funded by Sapheon Inc, Santa Rosa, Calif.

Author conflict of interest: Dr Mackay is a stockholder of Sapheon. Dr Proebstle is a consultant and stockholder of Sapheon.

Presented at the Twenty-fourth Annual Meeting of the American Venous Forum, Orlando, Fla, February 8-11, 2012.

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The editors and reviewers of this article have no relevant financial relationships to disclose per the Journal policy that requires reviewers to decline review of any manuscript for which they may have a conflict of interest.

2213-333X/$36.00

http://dx.doi.org/10.1016/j.jvsv.2012.09.010

implantable medical device in the United States for the treatment of arteriovenous malformations and intracranial arterial aneurysms,[13] as well as some other indications.

Upon intravascular injection, CA rapidly solidifies via a polymerization reaction and causes an inflammatory reaction of the vein wall.[14-16] In a swine model, at 30 days[17] after catheter-directed endovenous placement of CA in superficial epigastric veins, a granulomatous foreign body reaction was observed in the vein lumen. At 60 days,[18] also in swine, fibroblasts were seen invading the contents of the vein lumen, and 100% occlusion was observed. We report the first use of proprietary CA in humans to assess the efficacy and safety in patients with pathologic saphenous vein incompetence.

METHODS

The protocol for the study was approved by the National Committee of Bioethics and Health of the Dominican Republic (CONABIOS). All patients provided written informed consent.

Study design. This was a single-center, prospective, nonrandomized study of the feasibility, safety, and efficacy in the treatment of GSV incompetence in 38 patients with a proprietary CA adhesive (Sapheon, Santa Rosa, Calif). Initial screening included history and physical examination along with duplex ultrasound imaging to carefully map the sources of venous reflux in affected veins. Patients meeting inclusion and exclusion criteria, as listed in Table I and Table II, were included consecutively in the study. Baseline patient characteristics were scored with basic CEAP[19] classification, and severity of the disease was reported using the validated Venous Clinical Severity Score (VCSS).[20,21]

At 48 hours, and 1, 3, 6, and 12 months after treatment, clinical outcomes were assessed with a physical examination and duplex ultrasound imaging. Treatment success was defined as complete occlusion of the treated vein segment using duplex ultrasound imaging. According to Merchant's[22] original description, and in line with intersociety consensus,[23] any patency or recanalization, with or without reflux, in any treated segment >5 cm in length, was considered a treatment failure.

Procedure technique. The disposable Sapheon Closure System (SCS) includes 4 mL of Sapheon Cyanoacrylate Adhesive (SCA) and a Sapheon Delivery System (SDS; Fig 1). The SDS consists of a 7F introducer sheath/dilator, a 5F delivery catheter, a 3-mL syringe, and a dispenser gun. The 5F delivery catheter has a hydrophobic design to help prevent CA-mediated adhesion to the vein wall and a novel configuration with air-filled microchannels to enhance sonographic visibility. Engineers used mathematical volumetric calculations in cylindrical systems (venous tubes) to design the dispenser gun to deliver 0.08 or 0.16 mL of SCA with each trigger pull.

The operating surgeon performed the procedure without the assistance of an ultrasound technologist. Similar to EVTA, the patient's vasculature is mapped under ultrasound guidance, carefully assessing for areas of extensive tortuosity precluding catheter passage. The GSV is accessed percutaneously with a micropuncture introducer kit (Cook, Bloomington, Ind), followed by insertion of a 0.035-inch J guidewire (Cook). Ultrasound control (GE, Milwaukee, Wisc) is used to advance a 7F introducer sheath/dilator to the saphenofemoral junction (SFJ) and positioned 1.5 to 2.0 cm caudal to the SFJ.

The SCA is extracted with a 3-mL syringe, which is then attached to the delivery catheter. The catheter is primed with the dispenser gun to fill all but the final 3 cm of catheter tubing; this step ensures that the catheter tip is empty upon venous insertion to prevent premature

Table I. Inclusion criteria

- Men or nonpregnant women aged ≥21 years but <76 years.
- Venous reflux disease in the great saphenous vein diagnosed by clinical symptoms, with or without visible varicosities and confirmed by duplex ultrasound imaging.
- Candidate for surgical closure of a segment of the great saphenous vein.
- CEAP classification of ≥C_2.
- Ability to walk unassisted.
- Life expectancy of at least 18 months.
- Ability to attend follow-up visits.
- Ability to understand the investigational nature of the treatment and to provide written informed consent.

Table II. Exclusion criteria

- Previous surgical procedure (surgical, thermal, or chemical ablation) associated with the venous segment to be treated.
- Known sensitivity to the cyanoacrylate adhesive or positive reaction just before surgery (by injecting a small peripheral vein with the agent). The study surgeon will judge the need for the injection and the participant's reaction to the injection on clinical grounds.
- Diameter of index vein (supine) <3 mm or >12 mm in any segment.
- Formal duplication of the saphenous trunk in the index vein (accessory great saphenous vein segments allowed).
- Tortuous great saphenous vein, which in the opinion of the investigator will limit catheter placement.
- Hypercoagulable state.
- Local or systemic infection.
- Presence of incompetent perforators in the treatment length.
- Insulin-dependent diabetes.
- History of right ventricular failure.
- Leg obesity impairing the ability to gain access to the treatment leg and/or apply sufficient compression for treatment.
- Significant femoral or popliteal vein insufficiency.
- Documented history of superficial or deep thrombophlebitis.
- Additional procedures in the treatment leg likely required within 6 months after the investigational procedure.
- Varicosities secondary to pelvic or abdominal tumor.
- Current participation in another clinical study involving an investigational agent or treatment, or within the 30 days before enrollment.
- Significant arterial insufficiency demonstrated by the absence of an ankle pulse.
- Other concurrent medical or other condition (chronic or acute in nature) that in the opinion of the investigator may prevent safe participation or otherwise render the individual ineligible for the study.

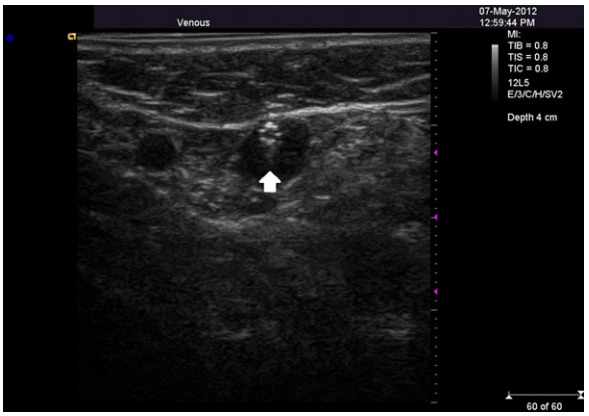

Fig 1. Ultrasound B-scan transverse section of the polytetrafluorethylene catheter tip (*white arrow*) shows six white dots corresponding to air-filled microchannels integrated into the catheter wall.

contact of SCA with blood. The primed delivery catheter is inserted into the introducer sheath and secured with a spin-lock mechanism. Using direct visualization with a standard linear ultrasound probe in the long axis, 5 cm of the catheter tip is exteriorized from the sheath and positioned 4 cm distal to the SFJ, a distance suggested by previously performed animal experiments.

Before delivery of the SCA adhesive, with the patient supine, the ultrasound transducer is positioned transversely, just cephalad to the catheter tip. Once positioned, using continual compression, two injections of 0.08 mL of SCA are delivered into the vein by depressing and holding the dispenser gun trigger. The entire delivery system is immediately retracted 3 cm, and the vein walls are coapted using additional compression over the treatment segment for 3 minutes. The next segment is then treated by repositioning the ultrasound transducer just cephalad to the catheter tip, occlusive compression is applied, and another 0.08 mL is delivered with one trigger depression, followed by 3-cm catheter pullback and compression of the treated vein for 30 seconds. This injection/retraction process is repeated until the entire length of the target vein segment is treated.

After venous closure is confirmed by ultrasound imaging, the catheter is removed and compression applied to the catheter entry site until hemostasis achieved. A single adhesive bandage is applied; neither compression stockings nor compression bandages are used.

Patients are discharged and instructed to resume normal activities but avoid strenuous exercise until the first follow-up visit at 24 to 72 hours. No ancillary procedures, such as phlebectomy or sclerotherapy, were permitted in the study protocol.

Patient characteristics. Patients (29 women [76.3%]) were a median age of 51 years (range, 26-77 years). The median body mass index (BMI) was 27.1 kg/m^2 (range, 21.5-45.3 kg/m^2). Patient comorbidities included hypertension in 11 (29%), obesity with BMI >25 kg/m^2 in 24 (63%), abnormal lipids in four (10.5%), diabetes in three (7.9%), and previous phlebectomy at the leg of study treatment in one (2.6%). One patient (2.6%) had a previous unsuccessful GSV laser ablation, which was not disclosed to the investigators at the time of study treatment.

By the CEAP classification, 14 patients (37%) were C_2, seven (18%) were C_3, 16 (42%) were C_4, and one (3%) was C_6. The average preprocedure VCSS was 6.0 ± 2.7 (range, 2-17). Mean preprocedural diameter of the GSV at the SFJ in the standing position was 8.0 ± 2.2 mm (range, 4.1-12.0 mm).

Statistical methods. The proportion of patients with continued complete closure of the GSV was calculated using Kaplan-Meier methods. Mean change from baseline in VCSS was evaluated using repeated-measures analysis of variance. Statistical calculations were performed with SAS software (SAS Institute, Cary, NC) and R software (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Thirty-eight limbs in 38 patients were treated by four different physicians during the single-center study. The four investigators were chosen due to their extensive experience with endovenous thermal ablation, clinical trials, and peer-reviewed publications. Training consisted of a didactic procedural overview, a tutorial on medical adhesives, a benchtop phantom demonstration of the procedure, and each operator performed the procedure in live swine before treating patients. The injection amounts were "fixed" by deliberate activation of the dispensing gun.

All 38 patients were available for follow-up at 1, 3, and 6 months, and 36 patients reached 12 months of follow-up. The same investigator performed all follow-up examinations, including the duplex ultrasound assessment. Mean treatment length was 33.8 ± 9.1 cm, the average volume of CA glue delivered, which depended solely on the treatment length, was 1.3 mL (range, 0.6-2.3 mL), and the average total treatment time was 21 minutes (range, 14-33 minutes). The GSV was accessed in 50% of patients below the knee, in 38% above the knee, and in 12% at knee level.

Safety. Nine adverse events occurred in eight patients (21%). Phlebitis of tributaries adjacent to the treated GSV appeared with mild pain and erythema in six patients (15.8%) and persisted for an average of 5.7 ± 4.2 days (range, 3-14 days). One patient developed a low-grade cellulitis that resolved with a 14-day course of oral antibiotics (Table III). One patient developed superficial thrombophlebitis in a solitary varix remote from saphenous treatment area that resolved spontaneously. One case of hyperpigmentation resulting from a treated vein coursing close to the skin was still visible at the 12-month follow-up visit.

Eight of the 38 patients (21.1%) showed thread-like thrombus extensions across the SFJ by ultrasound examination at the 48-hour follow-up. Mean protrusion length into the common femoral vein was 12.6 ± 9.9 mm (range, 3.5-35 mm). At 6 months of follow-up, all thrombus

Table III. Type and frequency of treatment-related adverse events

Pt	*Adverse event*	*Onset interval after treatment*	*Duration (days)*	*Specific treatment*
5	Varicophlebitis at remote location	Week 1	7	NSAID
8	Cellulitis	Week 1	14	NSAID, oral antibiotics
9	Phlebitis	Week 1	5	NSAID
14	Phlebitis	Week 1	5	NSAID
19	Phlebitis	Week 1	14	NSAID
23	Phlebitis	Week 1	3	NSAID, compression stockings
32	Phlebitis	Week 2	3	NSAID
38	Phlebitis, pruritus	Week 2	4	Antihistamines
38	Hyperpigmentation	Week 2	Ongoing	None

NSAID, Nonsteroidal anti-inflammatory drug.

extensions had resolved without clinical sequelae. Anticoagulation treatment was not performed at any time.

Anatomic success. Immediately after the procedure and at the 48-hour follow-up, complete occlusion of the treated vein segments were observed by duplex ultrasound imaging. During 12 months of follow-up, three patients presented with recanalization of >5-cm length at 1, 3, and 6 months, respectively. Life-table analysis (Fig 2, *A*) demonstrated a 12-month occlusion rate of 92.1%. One patient at the 1-month follow-up was found to have a partial recanalization originating at the saphenofemoral junction. This patient had complete recanalization at the 3-month follow-up. Two partial recanalizations with lengths of 10 and 7 cm were observed at 3 and 6 months, respectively, each at the midthigh level not propagating axial reflux. Thus, in summary, one patient recanalized, with axial reflux along the entire treatment length at the 3-month follow-up, leaving 97.3% of study-treated GSVs free from full-length recanalization at the 12-month follow-up (Fig 2, *B*). Recanalization did not occur in the patient with a prior failed endovenous laser procedure.

VCSSs. VCSSs were recorded at baseline and at all follow-up visits by the same physician according to the corresponding guidelines. The VCSS improved in the 36 patients who were seen at 12 months (Fig 3), with an average improvement from 6.1 ± 2.7 at baseline to 1.5 ± 1.4 at 12 months ($P < .0001$ by paired *t*-test). Compared with 39% of legs without edema before study treatment (Fig 4), 89% (34 legs) were observed without edema at 48 hours after treatment. Although at baseline all legs showed clinically relevant varicosities, at 6 months after study treatment, 17 legs (47%) were free from visible varicosities, and 13 (36%) showed only limited varicosities. At 12 months of follow-up, according to the VCSSs, the corresponding percentages improved further, with 50% (n = 18) of legs free from varicosities and an additional 25% (n = 9) with only limited varicosities.

DISCUSSION

Our method of endovenous CA delivery, with manual compression using an ultrasound transducer, followed by a waiting interval, capitalizes on the three phases of CA adhesive polymerization: an initial phase of rapid increase in tensile forces, lasting approximately 10 seconds; a second phase involving constant tensile force for up to 1 minute; and a final phase in which tensile force increases to attain complete polymerization.[24] The combined physical and chemical mechanism of action results in circumferential coaptation of the vessel wall, followed by adhesion, resulting in permanent vein closure. Several measures have been put into place to obviate inadvertent bonding of the catheter to the vein.[25] The immediate 3-cm pullback of the delivery system after each injection prevents intravascular catheter tip adhesion, and the delivery catheter has a proprietary hydrophobic nonstick surface. Lastly, the CA has been formulated to avoid premature polymerization.

In our recently published animal studies, where smaller veins were treated, only one injection was delivered to the segment closest to the SFJ.[17,18] Although vein closure was achieved in all swine, we wanted to ensure closure of the larger veins included in this human trial; therefore, two consecutive injections were placed 4 cm caudal to the SFJ. Vein closure was enhanced by the larger volume of glue delivered. By allowing 30 seconds to elapse between each injection, adhesion of the CA glue was also enhanced. This brief delay allowed completion of the second or possibly third phase of the polymerization reaction before the next injection was administered. In swine, a relevant thrombus within the vein lumen was not observed sonographically or histologically; instead, a chord of glue consistent with a chronic foreign body-type inflammatory response was seen. In chronologic sequence, we saw acute inflammation and foreign body giant cell formation, followed by complete intraluminal fibrosis.[18]

The use of endovenous CA adhesive for closure of the incompetent GSV was well tolerated by all patients in this first-in-man study. Sensitization to CA glue after dermal wound repair, as well as sensitization after occupational contact have been described,[26] and eosinophilic inflammation was also recently reported in a small proportion of ~2% after embolization of intracranial arteriovenous malformations.[27] However, a role for prospective testing of patients without a history of CA intolerance has not yet been defined.

At 12 months, 97.3% and 92.1% for freedom from complete or partial recanalization, respectively, is comparable to contemporary thermal ablation results,[3,4] for example, 1-year occlusion rates are 84% to 95% for foam, endovenous laser, or radiofrequency ablation.[4] In our

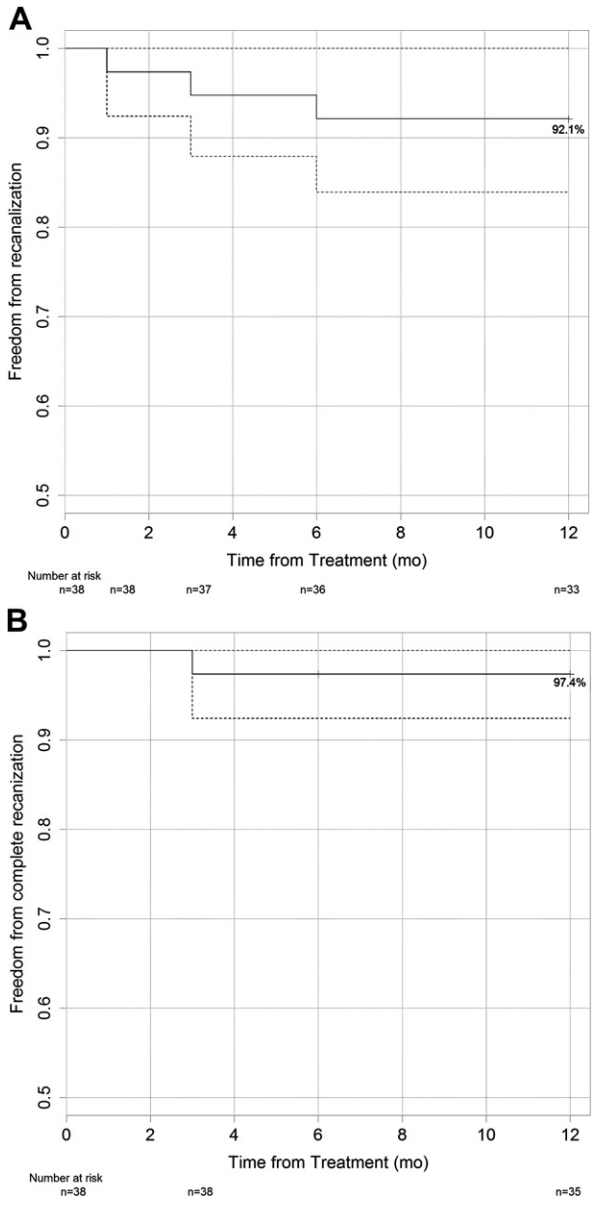

Fig 2. Life-table analysis shows **(A)** freedom from any recanalization and **(B)** freedom from complete recanalization of great saphenous veins after successful cyanoacrylate embolization. The *dotted lines* show the 95% confidence intervals. Patients at risk are given below the time axis. Standard error was <5% at all times.

study, only one of 38 limbs (2.6%) showed complete recanalization originating at the SFJ. The remaining two limbs with partial recanalization, with a maximum length of 10 cm, were located at midthigh and without hemodynamically significant reflux. Mimicking VCSS improvement after segmental radiofrequency thermal ablation as published recently,[28] VCSS improved after CA ablation in all 36 patients of this study during 12 months of follow-up from an average of 6.1 ± 2.7 at baseline to 1.5 ± 1.4. Lack of venous edema was recorded in 89% of legs at the

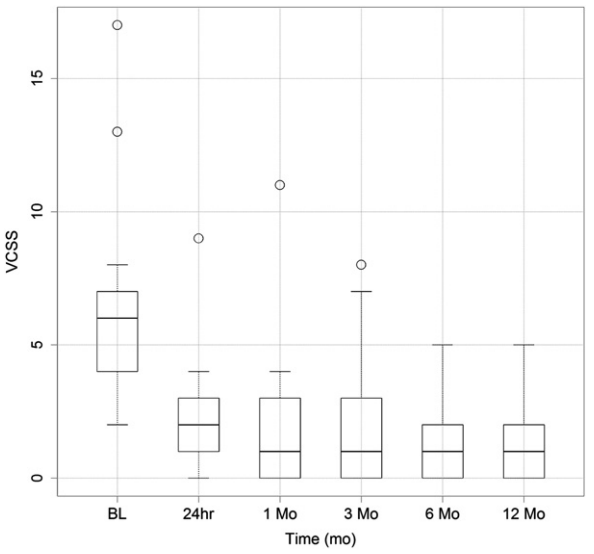

Fig 3. Box and whisker plot shows distribution of Venous Clinical Severity Scores (*VCCS*) of 38 patients during 12 months of follow-up. The *horizontal line* in the middle of each box indicates the median, and the *top and bottom borders* show Q3 and Q1, respectively, of the interquartile range (IQR). The *lower whisker* represents Q1 − 1.5 × IQR, and the upper whisker represents Q3 + 1.5 × IQR. The *circles* represent outliers.

48-hour follow-up, whereas at baseline, only 39% of legs were free from edema (Fig. 4). Moreover, all legs had visible varicosities at baseline, but at 12 months after study treatment, 50% of legs were free from visible varicosities and 25% of legs showed only limited varicosities in the absence of adjunctive phlebectomy or sclerotherapy. This certainly raises the question: How many vein patients are currently overtreated by the routine performance of

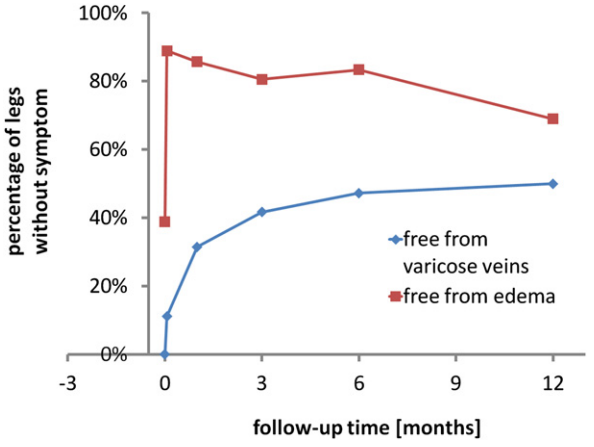

Fig 4. Percentage of legs free from varicose veins (*blue*) and edema (*red*) is shown during 12 months of follow-up. Results are obtained from the corresponding Venous Clinical Severity Score (VCSS) subscores for varicose veins and edema.

phlebectomy and sclerotherapy along with abolition of saphenous reflux? No serious treatment-related adverse events were observed at any time during follow-up.

At early follow-up, 21% of patients had thread-like-thrombus extensions across the SFJ. This was observed sonographically despite endovenous implantation of CA at a deployment distance of 4 cm from the SFJ. In this case, it may have been that the occlusive sheath, together with the strong compression applied by the ultrasound probe, forced the glue into a cephalad direction despite the small volume administered. Nevertheless, because conclusive studies about thrombus extensions after saphenous ablation are still missing, and moreover, no severe complications have been reported as a consequence, we decided not to treat any of the affected patients at any time with anticoagulation. However, to avoid this issue, in an ongoing European study, glue is deployed at a distance of 5 cm distal from the SFJ, and an additional pull back of 1 cm between the first and second trigger pull is done to allow more empty space to accommodate glue filling.

The endovenous implantation procedure involves a delicate balance of delivering an adequate volume of 0.09 mL of CA with the right speed under complete ultrasound control to occupy the entire cylindrical volume of the vein. This process is most critical at the patulous SFJ, ensuring that the CA adhesive has quickly solidified and polymerized to avoid migration into the common femoral vein.

The primary potential advantage of this novel vein closure technique is that it does not require perivenous tumescent anesthesia. Current thermal technologies necessitate the placement of perivenous tumescent fluid to dissipate the harmful heat that is generated. Although tumescent anesthesia successfully prevents perivenous tissue damage, it is time-consuming to administer and requires several noxious percutaneous injections.[29] In addition, the needle may unintentionally puncture the vein wall and create a perforation,[30] which may result in postprocedural pain and bruising. Endovenous CA implantation offers a solution to this drawback because perivenous tumescent anesthesia is omitted. The mild pain and inflammation experienced by only 13.2% of patients in this study was easily controlled with oral nonsteroidal anti-inflammatory drugs, and all were self-limited.

Another advantage is that patients are notoriously noncompliant with the recommended use of compression stockings; the patients in this study recovered well without them. With saphenous vein surgery, compression treatment for periods of 3 or 4 weeks did not seem to add clinical benefit for the patient compared with compression treatments of 1 week or 3 days, respectively.[31,32] Because this CA adhesive technique does not perforate the vein wall, our decision to omit postinterventional compression seemed logical. However, future randomized trials need to address this topic further. After surgical stripping or thermal and chemical endovenous ablation techniques, patient recovery may be supported by a short-term compression treatment.

CONCLUSIONS

After 1-year follow-up of the study cohort, we conclude that the procedure appears to be feasible and may provide efficacy similar to current endovenous ablation methods. Omitting multiple needle sticks for tumescent administration and eliminating the postinterventional compression therapy seemed appealing to patients. However, a weakness of the study is that patient numbers and follow-up intervals of the current study are still limited. Therefore, evaluation of efficacy, quality of life, and elimination of postinterventional compression treatment shall be the subjects of future randomized trials.

AUTHOR CONTRIBUTIONS

Conception and design: JA,
Analysis and interpretation: JA, TP
Data collection: JA, JJ, EM, CB, TP
Writing the article: JA, TP
Critical revision of the article: JA, JJ, EM, CB, TP
Final approval of the article: JA, JJ, EM, CB, TP
Statistical analysis: TP
Obtained funding: JA, JJ, EM, CB, TP
Overall responsibility: JA

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Submitted Jul 10, 2012; accepted Sep 22, 2012.