



A comparison of duplex ultrasound findings after cyanoacrylate embolization versus endovenous laser ablation of the great saphenous vein

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ABSTRACT

Background: Whereas numerous studies have demonstrated noninferiority of cyanoacrylate embolization (CAE) relative to endovenous laser ablation (EVLA), little is known about the natural history of the vein or the glue that is implanted. This study provides the first description of duplex ultrasound changes of the great saphenous vein (GSV) after CAE relative to EVLA as well as a pragmatic view of outcomes in clinical practice.

Methods: Patients treated with CAE and EVLA at our institution were matched by time of procedure and vein size. GSV diameter was measured at the saphenofemoral junction, mid thigh, and knee. Duplex ultrasound imaging was repeated after treatment in the same noninvasive laboratory with an identical protocol. Clinical data were collected by retrospective chart review.

Results: Of 481 eligible patients, 119 underwent postoperative duplex ultrasound imaging. Although there was a trend toward decreased vein diameter over time in CAE patients relative to their preoperative vein diameter, this failed to reach statistical significance at the mid thigh ($P = .32$) or at the knee ($P = .511$). In EVLA patients, as follow-up interval increased, the vein was less frequently visualized on ultrasound at the mid thigh ($P = .046$) and knee ($P = .038$). At >2 years of follow-up, >80% of EVLA patients had no visible vein segment. Anatomic recurrence was observed in 10.5% of CAE patients and 8.2% of EVLA patients, which was not statistically significantly different ($P = .60$). The majority of recurrence was observed in the presence of incompetent tributaries.

Conclusions: After CAE of the GSV, our results indicate that the glue cast remains for at least 3 years. Although our results suggest that the glue is broken down over time, this process is much slower than expected. In contrast, after EVLA, the vein tissue is remodeled and is no longer visible with time. In our study, which represents a pragmatic clinical population with a large (median, 9.2 mm) vein diameter, we again demonstrate no statistically significant difference in recurrence rates. Whereas CAE offers an attractive treatment option for GSV incompetence, the glue cast remains for a prolonged time, and longer follow-up studies than those currently available are indicated. (*J Vasc Surg: Venous and Lym Dis* 2019;7:824-31.)

Keywords: Varicose veins; Venous insufficiency; EVLT; N-butyl-cyanoacrylate; Nontumescent endovenous ablation; Tumescent endovenous ablation

Chronic venous disease affects 20% to 30% of the population and has a significant negative impact on quality of life.^{1,2} Therapy has shifted toward minimally invasive modalities, with both the Society for Vascular Surgery and National Institute for Health and Care Excellence guidelines recommending endothermal ablation as first-line therapy.³⁻⁵ Both endovenous laser ablation (EVLA) and radiofrequency ablation (RFA) require tumescent anesthesia, which is often the greatest source of discomfort during the procedure.⁶⁻⁸ This has driven

the advent of nontumescent, nonthermal techniques including cyanoacrylate embolization (CAE).

Cyanoacrylate is a medical-grade adhesive that rapidly polymerizes once it is brought into contact with blood.⁹ It has been previously used for treatment of cerebral arteriovenous malformations (AVMs), gastroesophageal varices, and type II endoleaks after endovascular aortic aneurysm repair.¹⁰⁻¹² When it is implanted in the great saphenous vein (GSV), it rapidly polymerizes and forms a glue cast.¹³ This disrupts the intima of the vessel and

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produces an inflammatory response, ultimately leading to fibrosis and closure of the vein segment.¹³

The first report of cyanoacrylate for treatment of venous insufficiency was published by Almeida et al in 2012.¹⁴ Subsequent studies with up to 3 years of follow-up have demonstrated anatomic success rates of 90% to 100%.¹⁴⁻¹⁷ Head-to-head studies have shown CAE to be noninferior to EVLA or RFA.^{6,7,18,19} In addition to similar success rates, patients experience decreased discomfort and ecchymosis.^{6,19}

There have been descriptions of the natural history of the GSV after RFA and EVLA.²⁰⁻²³ Although numerous clinical trials have been completed for CAE, no study to date has described the changes after treatment over time on duplex ultrasound. These studies provide a benchmark for expected findings on duplex ultrasound and help to understand recurrence. They also inform providers and patients about the natural history of the glue cast after implantation.

The primary objective of this study was to provide the first description of duplex ultrasound findings of the GSV after CAE relative to EVLA, with a focus on the change in the glue cast over time. We also describe the anatomic recurrences after these procedures in a clinical setting and the factors that contribute to anatomic recurrence.

METHODS

A retrospective cohort of patients was identified, all of whom had preoperative imaging performed before study initiation. Patients were identified and recruited during two time intervals. During the first interval, patients were recruited after the procedure and had been treated from July 2015 to January 2018. All patients treated with CAE were considered for participation on the basis of predetermined inclusion and exclusion criteria. Each CAE patient was matched to two patients treated with EVLA, meeting the same inclusion and exclusion criteria. Matching criteria included time since procedure (within 1 week) and vein size at the saphenofemoral junction (SFJ) on preoperative duplex ultrasound examination. To have data from patients immediately after the procedure, a second interval of recruitment occurred between April and August 2018. We enrolled patients before the procedure to undergo imaging immediately after treatment, before the patient's leaving the procedure room table. The same matching and inclusion and exclusion criteria were used throughout the study.

Once patients had been identified, we recruited patients to return for postoperative imaging. This was completed cross-sectionally. All patients who consented to inclusion had a one-time follow-up ultrasound examination. This provided a cohort of patients with a variable time that had elapsed between intervention and postoperative imaging. The change in patients' vein diameter

ARTICLE HIGHLIGHTS

- **Type of Research:** Single-center, cross-sectional cohort study
- **Key Findings:** After cyanoacrylate embolization of the great saphenous vein, there was a trend toward a reduction in vein diameter over time; however, this was slow and not significant when measured at the mid thigh ($P = .32$) or knee ($P = .51$).
- **Take Home Message:** After cyanoacrylate embolization, the glue cast appears to degrade over time; however, this process is slower than expected, with minimal change in vein diameter at 3 years.

was then analyzed relative to the length of time of the follow-up. In veins treated with cyanoacrylate, the lumen of the vein contains polymerized cyanoacrylate (glue cast), and changes in the vein diameter were used as a surrogate for changes in this glue cast.

Any patient receiving EVLA or CAE of the GSV with >0.5 second of retrograde flow relative to the physiologic direction on preoperative ultrasound was included in the study.

Exclusion criteria included the following: age <18 years; isolated treatment of the small saphenous vein or anterior accessory vein; prior ligation and stripping of the affected leg; inability to give informed consent; and inability or unwillingness to return for postprocedural imaging.

GSV diameter was measured by duplex ultrasound at the SFJ, mid thigh, and knee before treatment. Diameter was measured from adventitia to adventitia on cross-sectional images. Duplex ultrasound was repeated after treatment in the same noninvasive laboratory with an identical protocol. Clinical data were collected by retrospective chart review. All ultrasound and patient characteristic data were collected using standardized data collection forms.

Anatomic recurrence was defined as a patent segment of the GSV >5 cm, demonstrating reflux (>0.5 second of retrograde flow relative to the physiologic direction), that had been treated by either CAE or EVLA, in keeping with previous guidelines.^{3,24} Patients who were imaged immediately after therapy were not included in the analysis of recurrence. Ultrasound technicians were trained to make note of any large side tributaries, evidence of neovascularization, or new thrombus formation. Recurrence is considered proximal if the involved segment is from the junction to the mid thigh or distal if it is from the mid thigh to the knee.

Data analysis was conducted using Microsoft Excel 2017 version 16.9 (Microsoft, Redmond, Wash) and SAS software version 9.4 (SAS Institute, Cary, NC). Descriptive statistics were used to examine all outcomes of interest. Distribution of the data was first analyzed, and data following a normal distribution were presented as a

Table I. Baseline and outcome characteristics of patients receiving endovenous laser ablation (EVLA) or cyanoacrylate embolization (CAE)

	EVLA patients (n = 57)	CAE patients (n = 62)	P value
Female	68	74	.49
Age, years	53 (43-65)	49 (44-62)	.70
Vein size before procedure, mm			
SFJ	9.3 (2.2)	9.3 (2.1)	.96
Midhigh	6.4 (2.1)	6.7 (2.3)	.34
Knee	5.8 (3.0)	7.5 (7.9)	.17
Time of follow-up, months	14	16	.16
Co-treatment of anterior thigh tributary branch	1.75	6.45	.20
Access at or above knee	18	8	.13
No. of sclerotherapy sessions	1 (0-3)	2 (0-3)	.12
Anatomic success rate	91.8	89.5	.60
Reinterventions	3.5	4.8	.73

SFJ, Saphenofemoral junction.
Categorical variables are presented as percentage. Continuous variables are presented as mean (standard deviation) or median (interquartile range).

mean with standard deviation (SD). Non-normal data were presented as a median with the interquartile range. Fisher exact test was used to compare categorical outcomes, whereas Student *t*-test or a Wilcoxon rank sum test was used for continuous variables (depending on normality) on univariate analysis. In CAE patients, change in vein size over time was analyzed as a continuous variable using a linear regression model with only time as the dependent variable. Venous size was also analyzed with time categorized as 0 to 12 months, 12 to 24 months, and >24 months after the procedure using a one-way analysis of variance. The proportion of nonvisible vein segments in EVLA patients was analyzed using a χ^2 test.

The study protocol and informed consent process were reviewed and approved by the Hamilton Integrated Research Ethics Board. Patients were enrolled only after their informed consent.

RESULTS

Of patients treated between July 2015 and January 2018, there were 465 patients who were eligible, and attempted contact was made for enrollment. Of these patients, 108 returned for postprocedural ultrasound examination. The longest period of follow-up was 30 months. Two patients, one in each group, were eliminated at the time of follow-up as it was determined the GSV was not treated (one short saphenous and intersaphenous treatment and one anterior accessory vein treatment). Sixteen patients were contacted for immediate postprocedure duplex ultrasound examination, with 13 of these patients undergoing immediate postprocedural imaging. This gave a total of 57 EVLA patients and 62 CAE patients for analysis, with 18% of eligible EVLA patients and 39% of eligible CAE patients being successfully enrolled. A mean 2.03 mL (SD, 0.35 mL) of glue was used to treat a mean 46 cm (SD, 8.3 cm) of

vein in CAE patients. Average pullback time in EVLA patients was 247 seconds (SD, 122 seconds), with a mean energy of 1459 J (SD, 787 J).

In general, patients receiving CAE were younger, more likely to be female, and more likely to have co-treatment of the anterior thigh tributary (Table I). CAE patients were also more likely to have access below the knee and a larger below-knee vein segment. Diameter of the vein at both the SFJ and midhigh was similar between the groups.

CAE cohort. In CAE patients, we demonstrated a trend toward reduction in vein size over time at the midhigh and knee. Whereas there was a nonsignificant trend toward a relative reduction in size at the SFJ over time, we did not otherwise observe a consistent trend for absolute diameter change at the SFJ.

At the midhigh, we observed a trend toward decreased vein size over time (Fig 1) with a reduction in absolute vein diameter at year 2 relative to year 1 of 0.073 mm and at year 3 relative to year 1 of 0.3 mm ($F = 0.61$; $P = .55$). A similar trend was observed in the change in vein size relative to pretreatment diameter with a 41% reduction in vein diameter at 0 to 1 year, 45% reduction at 1 to 2 years, and 50% reduction at 3 years ($F = 0.93$; $P = .40$). Analysis was repeated using a linear regression model, which failed to reach statistical significance on either absolute vein diameter at midhigh ($P = .312$) or relative change in vein diameter ($P = .511$).

At the knee (Fig 2), we saw a similar trend; however, it was again nonsignificant. Absolute vein diameter was reduced by 0.61 mm and 1.02 mm at years 1 to 2 and >2, respectively, relative to year 1 ($F = 2$; $P = .14$). Relative reduction in vein diameter (from pretreatment vein diameter) increased from 36% to 49% to 54% at years 0 to 1, years 1 to 2, and years 2 to 3, respectively ($F = 1.32$; $P = .276$).

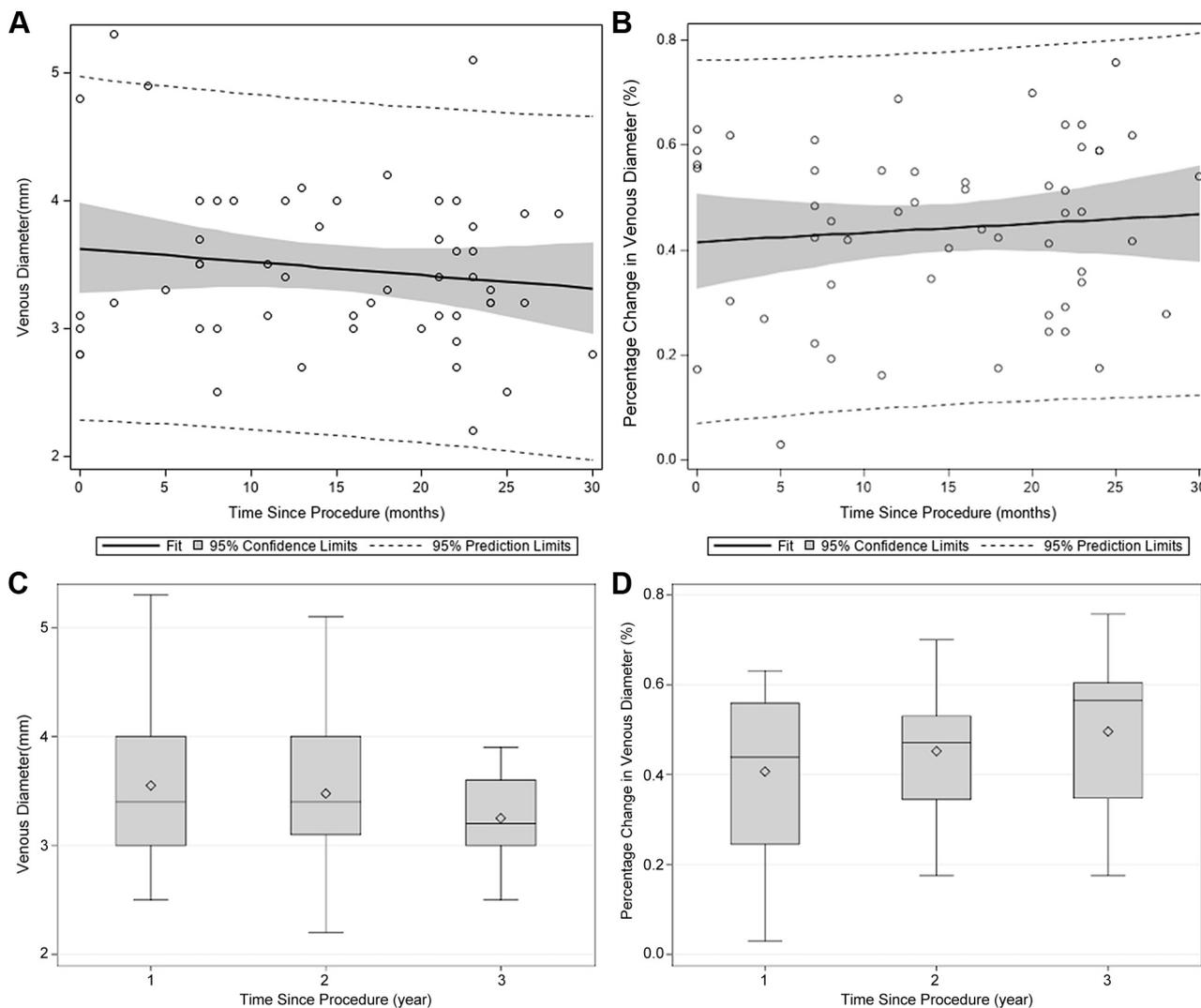


Fig 1. Venous diameter at the mid thigh vs time at follow-up for patients treated with cyanoacrylate embolization (CAE). **A**, Absolute vein diameter. **B**, Relative reduction (% decrease) from preprocedure vein diameter. **C**, Box plot of vein diameter at 1 year, 1 to 2 years, and 2 to 3 years of follow-up. **D**, Box plot of relative reduction (% decrease) from preprocedure vein diameter at 1 year, 1 to 2 years, and 2 to 3 years of follow-up.

EVLA cohort. In EVLA patients, a large proportion of vein segments at the mid thigh and knee were no longer visible on follow-up imaging. Over time, the proportion of patients with a vein segment no longer visible on duplex ultrasound increased both at the mid thigh ($P = .046$) and at the knee ($P = .0379$; Fig 3). Although we did see a trend toward a reduced vein size at the mid thigh over time, results were not as consistent as in CAE patients. Data were sparse as many patients no longer had visible vein segments to measure.

Treatment outcomes. We observed 8.2% of EVLA patients and 10.5% of CAE patients with anatomic recurrence (Table II). One patient in each group demonstrated a segment of recanalization; however, no reflux was present. As seen in Table II, patients who demonstrated anatomic recurrence had a larger vein diameter, 11.5 mm vs

9.3 mm (CAE, $P = .015$; EVLA, $P = .056$) and were older on average (CAE, $P = .50$; EVLA, $P = .14$). The most common segment of recurrence was a proximal recanalization. These segments of recurrence always occurred up to an incompetent mid thigh tributary. Likewise, the one distal segment in which we observed recurrence began at an above-knee incompetent tributary. The majority of these patients either had a revision procedure completed before follow-up or had one planned. Some patients, however, were minimally symptomatic from the recurrence and had elected not to undergo further procedures.

We observed no neovascularization in either EVLA or CAE populations in our study. We additionally did not observe any episodes of thrombus extension into the deep system from the GSV. One patient who underwent EVLA suffered a popliteal deep venous thrombosis over the period of follow-up.

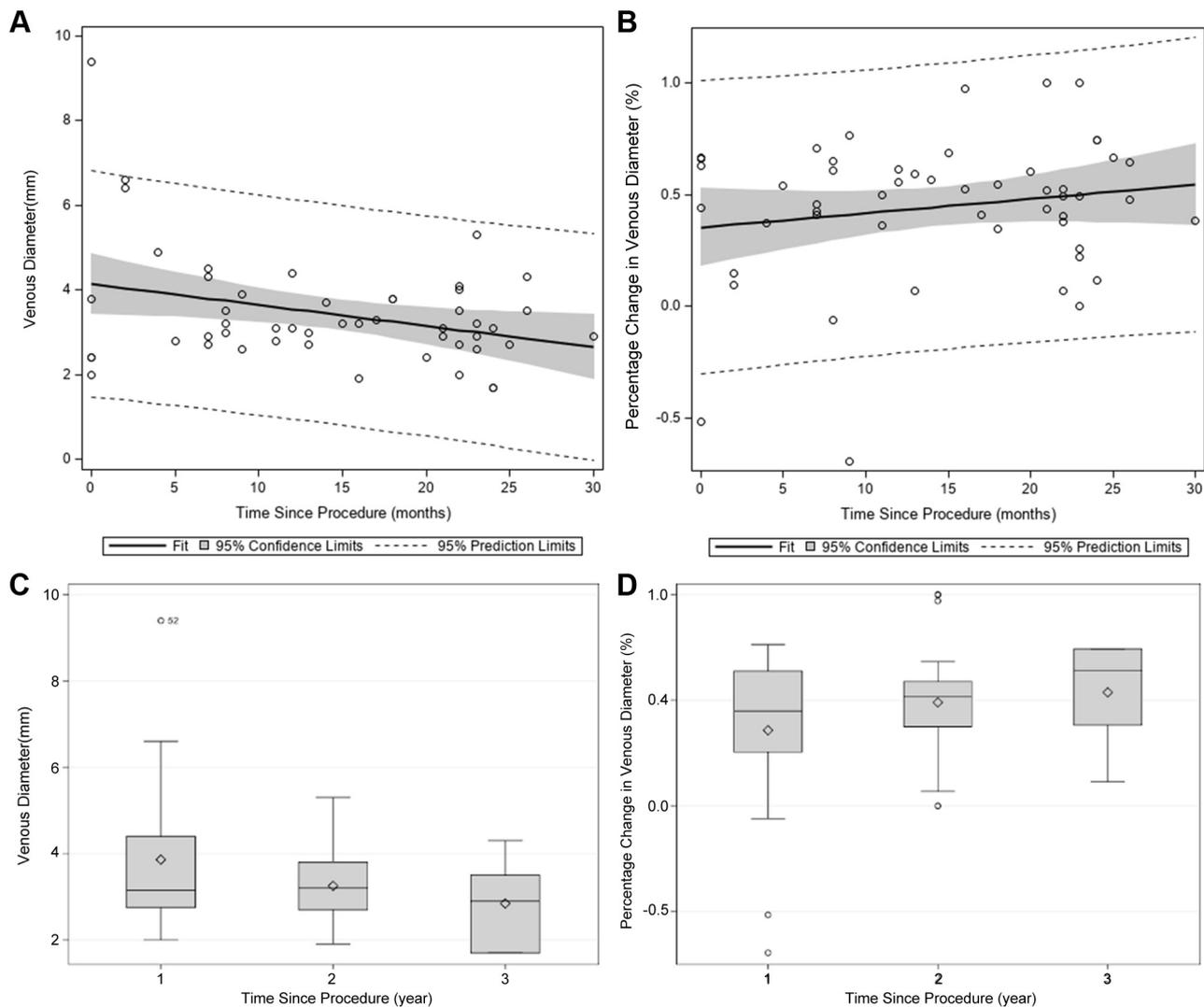


Fig 2. Venous diameter at the knee vs time at follow-up for patients treated with cyanoacrylate embolization (CAE). **A**, Absolute vein diameter. **B**, Relative reduction (% decrease) from preprocedure vein diameter. **C**, Box plot of vein diameter at 1 year, 1 to 2 years, and 2 to 3 years of follow-up. **D**, Box plot of relative reduction (% decrease) from preprocedure vein diameter at 1 year, 1 to 2 years, and 2 to 3 years of follow-up.

DISCUSSION

CAE of the GSV offers an attractive alternative to endothermal ablative procedures. Studies demonstrate decreased pain and ecchymosis and no requirement for tumescent anesthesia and postprocedural compression.^{6,7,18,19} Interest in CAE has generated many studies in the past 5 years, and results are promising to date. Head-to-head trials comparing CAE and endothermal methods have demonstrated noninferior anatomic recurrence rates.^{6,7,18,19} Follow-up studies have demonstrated anatomic success rates of 90% to 100% with 1 to 3 years of follow-up.^{6,7,18,19} Although there has been much investigation into the clinical efficacy of CAE, little is known about the natural history of the vein after treatment. To date, studies have focused on total recurrence rates, quality of life, and postprocedural outcomes. Our findings give physicians a reference to expected

anatomic changes on duplex ultrasound imaging, provide insights for recurrence, and allow patients to be informed about this novel procedure.

We demonstrated a trend toward reduction in vein size after CAE over time; however, this was small in magnitude and failed to reach statistical significance. We believe the best representation of the natural history of the vein is provided by the midhigh segment. Whereas the SFJ did demonstrate a reduction in size, we believe this is secondary to reduction of pressure and flow. During CAE, no glue is deposited at the SFJ. The knee segment is more variable in nature, often because of a greater number of tributaries in this region and proximity to the end of the segment that was treated.

Our results suggest that there may be a gradual resorption of the glue cast over time, but this process is very slow in nature. Almeida et al,²⁵ who conducted the first

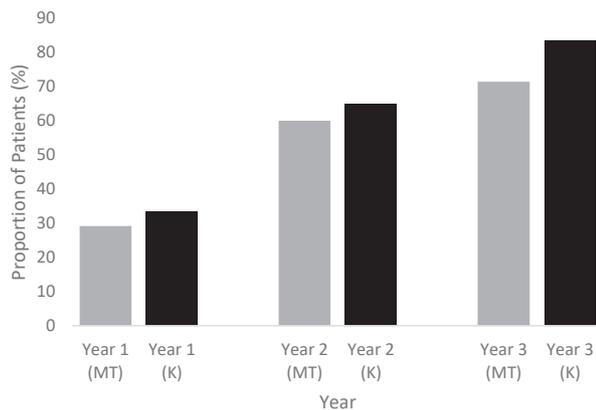


Fig 3. Proportion of patients undergoing endovenous laser ablation (EVLA) with a nonvisible vein segment at the midhigh (MT) or knee (K) at 0 to 1 year, 1 to 2 years, and >2 years of follow-up after the procedure.

studies on CAE of the GSV, had previously hypothesized that the glue cast decreased in size over time but never quantified this change. These findings are in contrast to EVLA; at >2 years after EVLA, a substantial number (>80%) of treated segments are no longer visible on duplex ultrasound. The outcome of cyanoacrylate within the body depends on the physiology of the specific area in which it is placed. In gastroesophageal varices, which lie close to a mucosal membrane, the cast erodes through the wall over time and is deposited in the gastrointestinal tract.¹⁰ In intracranial AVMs, the glue

cast has been demonstrated to be reduced in size over time.^{11,12} In the instance of an AVM, the cast may be exposed to arterial flow, which leads to the more rapid dissolution of the glue. These, however, are very different conditions from the GSV.

In pathology studies of AVM, there is evidence of cyanoacrylate deposited outside of the vascular structures, indicating that it is possibly primarily broken down over time.¹¹ We believe this would be a distinct form of cast breakdown, separate from what is seen in the presence of active flow, such as active AVMs; instead, there is “washout” of the glue. We hypothesize that a similar process of gradual, primary cast breakdown would occur with CAE of the GSV. This would explain our findings of a trend toward a size reduction of the glue cast in the absence of recurrence. This is much slower than anticipated, however. Changes in the glue cast after treatment of AVMs or varices are present within months to 2 years.^{10,12} It also indicates it is unlikely that any recurrence is secondary to primary breakdown of the glue cast as the rate is gradual. The cast appears to be stable in the body when it is not exposed to active flow.

Numerous factors may contribute to flow being reintroduced in proximity to treated segments. The recurrences we did observe always occurred in the presence of a patent incompetent tributary. Patients with recurrence in our study also tended to be older and to have larger vein diameters, in keeping with previous studies.^{26,27} Previous reports analyzing predictors of recurrence in both EVLA and CAE have determined vein diameter to be one if not the most important predictor of recurrence.^{26,27} In patients treated with cyanoacrylate, we believe larger veins are more prone to having inadequate volumes of cyanoacrylate deposited. Other authors have hypothesized this as well, and the Lake Washington Vascular VenaSeal Post-Market Evaluation (WAVES) study protocol allowed additional glue to be deposited at the time of the procedure at the interventionalist’s discretion.²⁸ In our practice, we will often inject additional cyanoacrylate at the site of tributaries and at the very least ensure that glue is deposited directly at the location. Further research into treatment of side branches, mechanisms of recurrence, and volume of cyanoacrylate required on the basis of vein diameter is warranted and may improve outcomes.

Regarding EVLA, our findings are consistent with those published in the literature.^{20,21,23} Unlike CAE, endothermal methods lead to scarring of the vein, leaving a fibrotic cord.^{20,21,23} Over time, this scar tissue is broken down, and the vein is no longer discernible from the surrounding tissue. We found that as time increases, the vein is increasingly less frequently observed, as would be expected in the remodeling process. This starkly contrasts with the changes observed after CAE, when the vein along with the glue cast continues to be detectable for years after the procedure.

Table II. Characteristics of patients demonstrating anatomic recurrence on follow-up duplex ultrasound examination

	EVLA patients	CAE patients
No. of anatomic failures	4 (8.2%)	6 (10.5%)
No. of recanalizations, no reflux	1	1
Age, years (IQR)	67 (54-72)	51 (44-72)
Vein size, mm		
SFJ	11.5	11.5
Midhigh	8.7	9.9
Knee	9.9	7.4
Segment of failure		
Partial proximal	3	3
Partial distal	0	1
Entire vein	1	2
Revision procedure before follow-up	2	3
Asymptomatic segments of recurrence	1	3
Revision procedure planned after follow-up	3	2

CAE, Cyanoacrylate embolization; EVLA, endovenous laser ablation; IQR, interquartile range; SFJ, saphenofemoral junction.

The recurrence rate we observed is consistent with that encountered in the literature but at the higher end. We did, however, have a large vein diameter at 9.2 mm relative to randomized controlled trials and many cohort studies, in which average vein diameter has been 6 to 8 mm.^{6,7,16,18,19,29} This study is primarily retrospective in nature with cross-sectional collection of postoperative duplex ultrasound imaging. There is also likely to be residual confounding between the EVLA and CAE groups, and therefore comparisons between these groups should be made with caution. Although not statistically significant, EVLA patients tended to be older, to be more commonly male, to have access below the knee, and to have shorter follow-up times. Although we had a similar number of EVLA and CAE patients, we matched in a 2:1 ratio and therefore had a far lower enrollment rates for EVLA patients (18% vs 40%). This is likely to be associated with a degree of selection bias and underlying differences between the two populations. The primary focus of this study was on anatomic changes in vein structure, not on efficacy of treatment, as this is best completed in clinical trials. This study does give insight in a more pragmatic setting, however, with larger vein diameters than in clinical trials. We believe this study provides important information to patients, who should be knowledgeable of the material placed during this procedure. Practitioners should be aware of the differences that occur after endothermal ablation, when the vein becomes undetectable over time, and CAE. Although randomized controlled trials to date have demonstrated noninferiority of CAE relative to EVLA, cyanoacrylate is a relatively novel procedure, with most follow-up in the literature reaching 3 years. The glue cast appears to be inert, but it does represent a foreign material in the body that remains present for many years. This may be particularly relevant for a procedure often performed in younger individuals; in our study, patients had a median age of 49 years. The body of literature as it stands today favors a positive safety profile, and the decreased discomfort relative to tumescent-based procedures may make this a preferred choice for some patients. Long-term follow-up studies, past the 3-year interval, however, are important to monitor safety and efficacy of this therapy in the long term.

CONCLUSIONS

After CAE of the GSV, the glue cast remains for at least 3 years. Whereas there is a trend toward reduction in the size of the glue cast, it is slow and not statistically significant. This is in contrast to EVLA; at >2 years after EVLA, >80% of patients no longer have a visible segment of vein. This report also gives a pragmatic view of patients treated in clinical practice, with a larger median vein size than in most studies. We demonstrated no statistically significant difference in anatomic recurrence rates in keeping with previous reports. Whereas CAE offers

an attractive method for treating GSV incompetence, patients and practitioners should be aware that the glue cast remains for an extended time, and longer follow-up studies are indicated.

AUTHOR CONTRIBUTIONS

Conception and design: BM, FE, BC, DS, TR

Analysis and interpretation: BM, FE, DS, TR

Data collection: BM, KA, MA, JN

Writing the article: BM

Critical revision of the article: BM, FE, KA, MA, JN, BC, DS, TR

Final approval of the article: BM, FE, KA, MA, JN, BC, DS, TR

Statistical analysis: BM

Obtained funding: Not applicable

Overall responsibility: BM

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