Adjunctive techniques to minimize thrombotic complications following microfoam sclerotherapy of saphenous trunks and tributaries

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ABSTRACT

Objective: Thrombus extension into the deep venous system following superficial vein chemical ablation with Varithena polidocanol microfoam has been reported. The objective of this study was to assess the effect of intraoperative improved techniques during treatment for patients with symptomatic varicose veins and their impact on extension of thrombus into deep veins.

Methods: A retrospective review of a prospectively maintained database was performed. All patients who underwent endovenous chemical ablation with polidocanol microfoam (Varithena, Boston Scientific, Marlborough, Mass) for symptomatic superficial axial and tributary vein reflux were identified. Patients had postoperative duplex (48-72 hours) scanning after the procedure; those who did not adhere to the recommended follow-up were excluded. Demographic data, CEAP Classification, Venous Clinical Severity Score, procedure details, and follow-up data were abstracted.

Results: Between April 2018 and August 2020, 157 limbs in 122 patients were treated with Varithena microfoam; 129 limbs in 99 patients met our inclusion criteria. Veins treated included the great saphenous vein (n = 89), anterior accessory saphenous vein (n = 15), small saphenous vein (n = 14), and tributary veins (n = 56). Adjunctive techniques during treatment included intraoperative elevation of the limb to greater than 45°, ultrasound mapping and digital occlusion of large perforator veins, limitation of foam volume per session, injection of sterile saline before treatment, and compression of the limb in the elevated position. The preoperative Venous Clinical Severity Score was 11.4 and decreased after treatment to 9.7. The immediate closure rate was 95% with 81% overall symptomatic relief at last follow-up. The mean follow-up was 113.5 days for the entire cohort; two limbs (1.5%) required postoperative anticoagulation for thrombus extension into the deep venous system (common femoral vein n = 1; popliteal vein n = 1) postoperatively for a mean of 22 days. Both resolved with anticoagulation. One asymptomatic limb developed a femoral vein deep venous thrombosis and one symptomatic late deep venous thrombosis was noted 4 months after the procedure. Postoperative pain and phlebitis were reported in 15.6% and 14.8% of patients, respectively, and all had resolved at last follow-up. No pulmonary emboli were noted and no neurologic or visual adverse events were recorded.

Conclusions: Adjunctive techniques during microfoam ablation decreased thrombotic complications in our series compared with those reported in earlier phase III clinical trials. Excellent early closure and symptomatic improvement were also noted. Endovenous microfoam ablation with Varithena is a safe and effective nontumescent, nonthermal alternative to laser and radiofrequency ablation. (J Vasc Surg Venous Lymphat Disord 2021;9:904-9.)

Keywords: Varicose veins; Venous ulcer; Venous insufficiency; Edema

Varithena polidocanol microfoam (Boston Scientific, Marlborough, Mass) was approved by the U.S. Food and Drug Administration in 2013 for the treatment of incompetent veins associated with the great saphenous system. It consists of a commercially developed, low nitrogen, 1% polidocanol foam used for nonthermal, nontumescent closure of refluxing, symptomatic superficial truncal and tributary veins. Despite the demonstration of symptomatic improvement, early phase III clinical trials for Varithena reported the incidence of posttreatment thrombotic adverse events to be up to 13.6%[1-3] (Table I). In our series, we report our outcomes following the performance of adjunct techniques. aimed at decreasing postprocedure thrombotic complications, which were used during endovenous microfoam ablation of truncal and tributary veins. These techniques included the following:

1. Preoperative duplex ultrasound examination performed by our vascular ultrasound laboratory and

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also performed by the proceduralist at the time of operation. Large perforator veins were localized and mapped before injection of microfoam.
2. Limb elevation to greater than 45°.
3. Injection of 10 mL of sterile saline before microfoam infusion to displace blood from the vein. In theory, the purpose is to limit the volume of foam administered and maximize microfoam contact with luminal surface.
4. Attempted limitation of microfoam volume to 5 mL or less (if possible),
5. Compression of the axial vein 5 cm caudal to the saphenofemoral or saphenopopliteal junctions and compression of perforator veins during microfoam injection.
6. Dorsiflexion and plantar flexion of the ipsilateral foot and ankle for 20 repetitions after microfoam injection.

These modifications were not specifically outlined in the prior phase III clinical trials for Varithena.[1-3]

ARTICLE HIGHLIGHTS

- **Type of Research:** Single-center retrospective cohort study
- **Key Findings:** There were 129 limbs in 99 patients were treated with Varithena chemical ablation for refluxing superficial axial and tributary veins. Adjunctive techniques during Varithena chemical ablation resulted in a proximal deep vein thrombus extension incidence of 1.5% and an overall adverse deep venous thrombotic event incidence of 3.0%.
- **Take Home Message:** Adjunctive techniques during chemical microfoam ablation for symptomatic varicose veins facilitate lower deep venous thrombotic complications than reported in early phase III clinical trials.

METHODS

Approval was obtained by our institutional review board for the implementation and publication of this study. The requirement for patient consent was waived by the institutional review board. All patients who underwent endovenous chemical ablation with 1% polidocanol microfoam (Varithena, Boston Scientific) for symptomatic superficial axial and tributary vein reflux were identified through a prospectively maintained database. Patients who did not undergo postoperative ultrasound at 48 to 72 hours were excluded from the study. Demographic data, CEAP Classification, Venous Clinical Severity Scores (VCSS), procedure details, and follow-up data were abstracted.

All procedures were performed by vascular surgeons in an ambulatory venous center under local anesthesia. Inclusion criteria included patients with symptomatic varicose veins associated with either saphenofemoral or saphenopopliteal vein reflux. Asymptomatic (CEAP clinical class 0 and 1) were excluded from the study. Ultrasound-guided venous access was obtained with either a 4F micropuncture needle and 4F sheath or with a 21G butterfly needle. We performed the following adjunctive techniques for our ablation procedures. After sheath or needle placement, the limb was elevated to greater than 45° using a tilt table to place the patient in steep Trendelenburg position. Two individuals are required to perform the procedure. The surgeon compressed the axial vein undergoing ablation and injected the microfoam. An assistant withdrew the microfoam from the canister and also digitally compressed previously marked perforator veins with sterile technique. Ten milliliters of sterile saline were injected into the treated veins while in the elevated position to greater than 45° followed by the Varithena injection. Microfoam volume was limited to 15 mL or less per session and was usually 5 mL or less in a single site. Large perforator veins were carefully identified during preoperative and intraoperative vein mapping and occlusive digital pressure was held over them during microfoam injection (Fig 1, *A*) For truncal veins, pressure was held 5 cm caudal to either the saphenofemoral or saphenopopliteal junctions using the ultrasound transducer for 5 minutes. During this time, the patient was instructed to dorsiflex and plantar flex the ankle for 20 repetitions. Immediately after the procedure, the femoral and popliteal veins were evaluated for acute thrombus with intraoperative ultrasound examination, and compressibility was assessed. The treated limb was compressed in the elevated position (>45°) with abdominal pads overlying the treated veins, using long-stretch bandages.

All patients underwent duplex ultrasound examination of the entire deep and superficial venous systems within 48 to 72 hours after the procedure to ensure successful superficial vein closure and to rule out deep venous thrombosis (DVT). Patients were instructed to wear 20 to 30 mm Hg thigh high compression stockings continuously for 14 days after their procedure Patients were then scheduled for a 6-week postoperative visit and assessment of post-treatment VCSS was calculated at this time by the vascular surgeon who performed the initial procedure. Symptomatic patients were scheduled as soon as possible. After the initial postoperative ultrasound examination, routine ultrasound examinations were not performed unless the patient presented with leg symptoms (ie, persistent pain, redness, tenderness, and swelling). Postoperative leg pain, edema, and phlebitis (defined as redness and or tenderness at the site of a thrombosed vein) were assessed clinically by the vascular surgeon who performed the procedure, and this situation was monitored at each postoperative visit. All patients treated with microfoam ablation are counseled regarding long-term compression stocking

Table I. A comparison of adverse thrombotic events (*ATEs*) across studies

Study	Common femoral or popliteal extension	Other DVT	Percentage of total ATEs in study	Symptomatic	Patients with ATEs anticoagulated
VANISH 1[1]	5.5	3.3	8.8	22	Not stated
VANISH 2[2]	3.9	6.6	10.5	33	50
Gibson, et al[3]	4.1	9.5	13.6	None	20
Jimenez, et al (current study)	1.5	1.5	3.0	0.78	100

DVT, Deep venous thrombosis.
Values are percent.

use (minimum of 20-30 mm Hg strength), leg elevation, avoidance of prolonged standing, exercise, and weight management.

RESULTS

Between April 2018 and August 2020, 157 limbs in 122 patients were treated with Varithena microfoam. All patients were treated for symptomatic varicose veins; 129 limbs in 99 patients met the inclusion criteria. Twenty-four patients (28 limbs) were excluded because they did not undergo an early (48-72 hour) postoperative ultrasound examination. The mean patient age was 66.5 ± 13 years. Sixty-five patients (66%) were female. The distribution of patients by preoperative CEAP clinical stage are demonstrated in Table II. The mean preoperative VCSS score was 11.4 ± 4.9. The mean follow-up was 113.5 days for the entire cohort. Eighteen patients were treated while on chronic anticoagulation; 14 had a history of prior DVT. Anticoagulation was not held during Varithena ablation procedures and no specific thrombosis prophylaxis was used for this cohort of patients.

Veins treated included the great saphenous vein (n = 89), anterior accessory saphenous vein (n = 15), small saphenous vein (n = 14), and tributary veins (n = 56). The mean maximal truncal vein diameter was 7.2 ± 5.4 mm. The mean maximal tributary vein diameter treated was 5.4 ± 1.9 mm. The mean volume of microfoam used per session was 7.6 ± 3.3 mL. The early (48-72 hours) closure rate was 95%; six veins (4%) partially closed. One saphenous vein (1%) failed to close after the first treatment but closed after a second treatment.

Twenty patients (15.6%) reported postoperative pain; 19 patients (14.8%) developed early postoperative superficial phlebitis and 2 patients (1.6%) complained of postprocedure swelling. Subjective assessment of symptoms was obtained by history and physical examination by the vascular surgeon who performed the initial procedure. A visual analog scale was not used. No postoperative infections were identified. The mean VCSS decreased after treatment to 9.7 ± 4.6. Overall, 105 patients (81%) reported overall symptomatic improvement at their last follow-up visit (Fig 2, *A* and *B*).

Table III demonstrates the occurrence of adverse deep vein events anatomically by axial vein treated. Two limbs (1.5%) were noted to have nonocclusive thrombus extension into the common femoral vein and popliteal vein by duplex ultrasound examination performed 48 hours after their procedures. Thrombus resolved completely in both patients by duplex ultrasound examination after 32 and 12 days of novel oral anticoagulant therapy. Both patients were asymptomatic. One asymptomatic patient was noted to have an occluded paired femoral vein (48 hours after the procedure) and resolved after 3 months of oral anticoagulation. The incidence of early postprocedure thrombotic events after microfoam closure was 2.3%. One patient developed leg swelling and was diagnosed with a femoropopliteal DVT 4 months after ablation of her anterior accessory great saphenous vein, after an international airplane flight (a long haul flight lasting

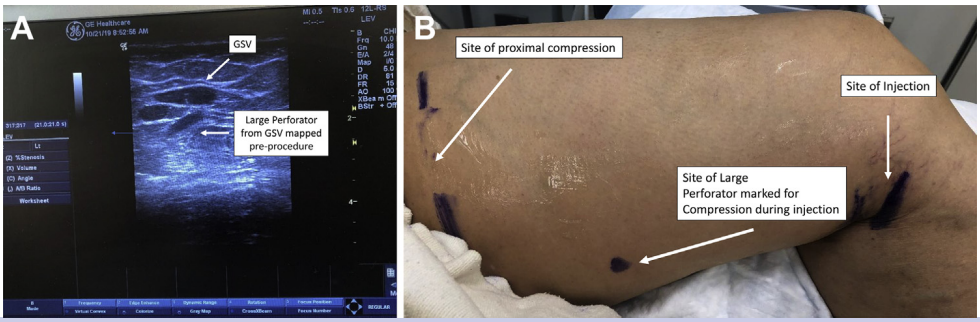

Fig 1. A, A large perforator vein arising from the great saphenous vein is vein mapped before microfoam ablation. **B,** The site of the perforator vein is marked on the skin and is compressed during microfoam ablation to decrease the risk of Varithena migration into the deep venous system

Table II. Distribution of preoperative CEAP clinical scores

CEAP clinical class "C"	Preoperative
1	0
2	40 (31)
3	21 (16.3)
4	23 (17.8)
5	13 (10.1)
6	32 (24.8)

Values are number (%).

>4 hours). She was later diagnosed with a heterozygous factor V Leiden mutation and completed a 3-month course of oral anticoagulation. The incidence of adverse deep vein thrombotic events during the entire study period was 3%. No patient developed pulmonary emboli or an acute adverse neurologic or visual event during the study period.

DISCUSSION

Despite approval by the U.S. Food and Drug Administration, the phase III clinical trials for Varithena ablation for saphenofemoral incompetence demonstrated thrombotic complication rates higher than contemporary reported rates after thermal ablation.[1-5] A study from our institution reporting outcomes for 1000 patients after radiofrequency ablation of the saphenous vein demonstrated a postprocedure thrombotic complication rate of 1.8%.5 The Vanish-2 study of microfoam by Todd et al[2] reported an incidence of adverse deep vein thrombotic events of 10.4% and thrombus extension into the common femoral vein occurred in 3.9% of the study population. In a similar study by Gibson et al,[3] the incidence of thrombus extension into the common femoral vein after microfoam ablation was 4.1%. The postoperative isolated DVT was noted in 9.5% of patients treated with 1% polidocanol microfoam. No pulmonary emboli occurred in either study.

Our rate of nonocclusive extension of thrombus into the deep venous system after microfoam saphenous ablation (1.5%) seems to be markedly lower than the incidence of thermal ablation reported in the current peer-reviewed literature, whether with radiofrequency or laser ablation of the saphenous veins.[6,7] In our series, one patient developed an early postoperative isolated DVT in a paired femoral vein that was asymptomatic and found incidentally on her postoperative duplex ultrasound examination. Only one of the two paired femoral veins demonstrated thrombosis while the other remained patent. Only one symptomatic DVT occurred in one study patient, 4 months after her procedure. Her DVT occurred after a transatlantic plane ride lasting more than 4 hours (Table III). She was subsequently diagnosed with a heterozygous factor V Leiden mutation that was undiagnosed at the time of her initial procedure.

We performed adjunctive techniques during endovenous microfoam ablation that were not specified in the early phase III trials and were aimed to decrease the incidence of thrombotic complications in our cohort. We attempted to minimize the amount of microfoam used per session; in our series, the mean volume of microfoam used was 7.6 mL and the maximum amount used was 15 mL per session. We attempted to limit foam volume to 5 mL or less whenever possible. Injection of sclerosant foam systemically into the superficial venous system is a less directed technique than thermal ablation, allowing a higher theoretical risk of microfoam migration into the deep venous system. In the series by Gibson et al,[3] the initial maximum volume of microfoam allowed per session was 30 mL or less and the mean volume used per patient was 16.5 mL.[3] The maximum amount of microfoam was amended midstudy to 15 mL or less after a 26% incidence (5 DVT of the initial 19 patients) of early DVT was noted.[3]

During treatment of truncal veins, care was taken to maintain microfoam within the superficial vein(s) being treated. We identified large perforator veins during preoperative and intraoperative vein mapping with ultrasound imaging. The perforators were carefully marked with a surgical pen and digitally occluded during foam injection. Digital pressure was also held, using a transducer, 5 cm caudal to either the saphenofemoral or saphenopopliteal junction, as well as over large perforator veins to avoid microfoam migration into the deep venous system.

The initial axial vein closure incidence of 95% compares favorably with current studies analyzing outcomes for thermal and microfoam ablation, despite using a relatively decreased volume of foam compared with earlier Varithena studies.[1-3,5] Adjunctive techniques used to increase maximal microfoam contact with the vein lumen and improve venous closure included the injection of 10 mL of sterile saline into the veins before foam ablation as well as administration of microfoam into the leg in steep Trendelenburg position with the leg elevated to higher than 45°, and, last, application of compression bandages with the leg raised. The purpose of the saline injection with the leg elevated position before microfoam infusion is to displace blood from the vein and, in theory, maximize microfoam contact with the vein's luminal surface. In our study population, 81% of patients reported subjective symptomatic relief after microfoam ablation and the mean VCSS decreased after treatment.

A recent article by Kim et al[8] reports a similar postprocedure incidence (1.7%) of DVT in a smaller cohort of patients undergoing microfoam ablation. Of note, the DVT occurred owing to an unidentified perforator vein during treatment. Our protocol strictly outlines the careful ultrasound identification of perforator veins before Varithena injection. The authors describe some similar techniques,

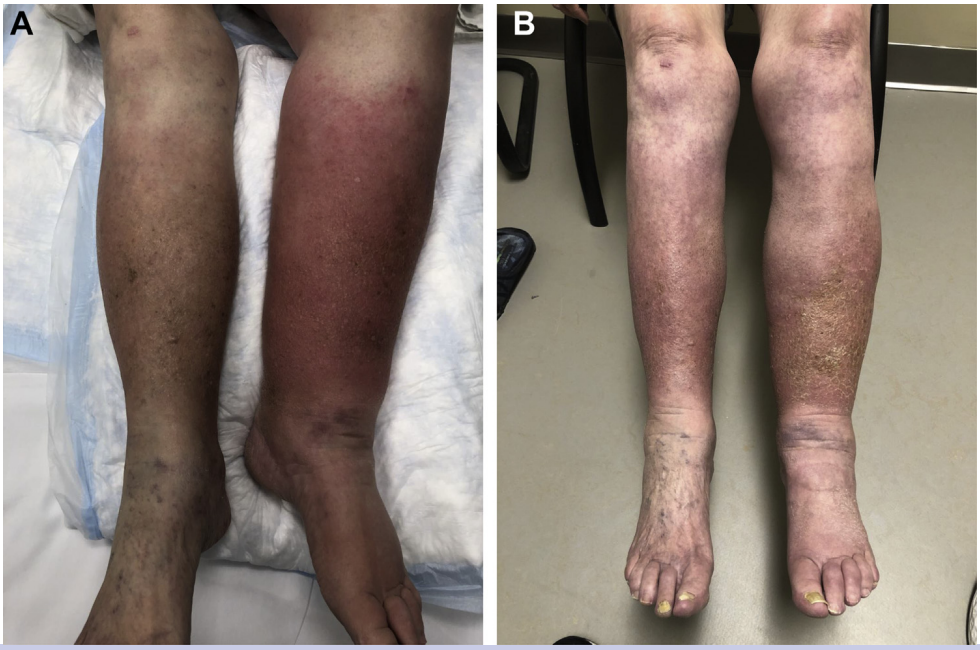

Fig 2. A, A 70-year-old woman presented with severe left leg edema and lipodermatosclerosis before microfoam ablation. **B,** Significant clinical improvement 17 days following successful microfoam ablation of her left great saphenous vein. During this postoperative period, the patient also wore graded compression stockings (20-30 mm Hg) and periodically elevated her leg.

such as leg elevation to greater than 45° and plantar and dorsiflexion of the ipsilateral ankle; however, the mean volume of microfoam used in their series was higher (11.2 mL vs 7.6 mL in our series) and sterile saline injection was not used.[8] In an earlier series of patients treated with leg vein sclerotherapy with physician-compounded foam, a 1.5% incidence of DVT was reported.[9] On regression analysis, there was a statistically increased risk of DVT when more than 10 mL of foam was used. This finding supports our advocacy for keeping the volume of microfoam as close to 5 mL as possible per session. Attempts to limit microfoam volume in our series include elevating the vein to decrease vein diameter and injection of sterile saline to displace blood from the vein and maximize the microfoam contact with the luminal surface.

A limitation of our study is our relatively short period of follow-up. However, the primary outcome measure of our study was postoperative thrombotic events. Our study period is adequate, because the majority occur early after treatment. We are planning to report our long-term symptomatic results in a future study. Another limitation of our study compared with phase III clinical trials is the nonrandomized, retrospective study design. It is possible that selection bias may have contributed to the outcomes in our study compared with prior randomized studies. Our study also used postoperative duplex ultrasound examinations to evaluate the entire deep venous system 48 to 72 hours after microfoam ablation. Additional ultrasound studies are not routinely performed unless patients returned with recurrent or new symptoms. Thus, it is possible that asymptomatic DVTs later in the study period may not have been detected. Despite clear documentation of overall subjective improvement by vascular surgeons and a decrease in VCSS scores in our patient cohort, our study did not use formal quality of life (ie, VEINES-QOL/SYM, VVSymQ) questionnaires.

Table III. Occurrence of adverse deep vein events by axial vein treated

Vein treated	No. of limbs	No. of early adjacent deep vein thrombus extension	No. of early remote deep venous thrombus	No. of late remote deep venous thrombus
GSV	89	1	1	0
Anterior accessory saphenous vein	15	0	0	1[a]
Small saphenous vein	14	1	0	0

GSV, Great saphenous vein.
[a]Femoropopliteal deep venous thrombosis occurred 4 months after microfoam injection following a long-haul airplane flight. She was later found to be heterozygous for factor V Leiden.

CONCLUSIONS

With the performance of adjunctive techniques described, our study results demonstrate minimal deep venous thrombotic adverse events after microfoam ablation for incompetent axial and tributary veins. Excellent early closure and symptomatic improvement were also noted. Endovenous microfoam ablation with Varithena is a safe and effective nontumescent, nonthermal alternative to laser and radiofrequency ablation.

AUTHOR CONTRIBUTIONS

Conception and design: JJ, TC, SF
Analysis and interpretation: JJ, PL, KW, TC, SF, DR
Data collection: JJ, TC
Writing the article: JJ, PL, KW
Critical revision of the article: JJ, PL, KW, TC, SF, DR
Final approval of the article: JJ, PL, KW, TC, SF, DR
Statistical analysis: Not applicable
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Overall responsibility: JJ

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