Factors that influence perforator thrombosis and predict healing with perforator sclerotherapy for venous ulceration without axial reflux

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Objective: **Refluxing perforators contribute to venous ulceration. We sought to describe patient characteristics and procedural factors that (1) impact rates of incompetent perforator vein (IPV) thrombosis with ultrasound-guided sclerotherapy (UGS) and (2) impact the healing of venous ulcers (CEAP 6) without axial reflux.**

Methods: **A retrospective review of UGS of IPV injections from January 2010 to November 2012 identified 73 treated venous ulcers in 62 patients. Patients had no other superficial or axial reflux and were treated with standard wound care and compression. Ultrasound imaging was used to screen for refluxing perforators near ulcer(s). These were injected with sodium tetradecyl sulfate or polidocanol foam and assessed for thrombosis at 2 weeks. Demographic data, comorbidities, treatment details, and outcomes were analyzed. Univariate and multivariable modeling was performed to determine covariates predicting IPV thrombosis and ulcer healing.**

Results: **There were 62 patients (55% male; average age, 57.1 years) with active ulcers for an average of 28 months with compression therapy before perforator treatment, and 36% had a history of deep venous thrombosis and 30% had deep venous reflux. At a mean follow-up of 30.2 months, ulcers healed in 32 patients (52%) and did not heal in 30 patients (48%). Ulcers were treated with 189 injections, with an average thrombosis rate of 54%. Of 73 ulcers, 43 ulcers (59%) healed, and 30 (41%) did not heal. The IPV thrombosis rate was 69% in patients whose ulcers healed vs 38% in patients whose ulcers did not heal ($P < .001$). Multivariate models demonstrated male gender ($P = .03$) and warfarin use ($P = .01$) negatively predicted thrombosis of IPVs. A multivariate model for ulcer healing found complete IPV thrombosis was a positive predictor ($P = .02$), whereas a large initial ulcer area was a negative predictor ($P = .08$). Increased age was associated with fewer ulcer recurrences ($P = .05$). Predictors of increased ulcer recurrences were hypertension ($P = .04$) and increased follow-up time ($P = .02$). Calf vein thrombosis occurred after 3% (six of 189) of injections.**

Conclusions: **Thrombosis of IPVs with UGS increases venous ulcer healing in a difficult patient population. Complete closure of all IPVs in an ulcerated limb was the only predictor of ulcer healing. Men and patients taking warfarin have decreased rates of IPV thrombosis with UGS. (J Vasc Surg 2014;59:1368-76.)**

Incompetent perforator veins (IPVs) have long been associated with venous disease and ulceration. Perforator veins in and around the ankles are particularly vulnerable to incompetence, and venous hypertension in this area creates edema, skin discoloration, and ulceration.[1] Compression is the mainstay of treatment for venous incompetence and reflux. However, even in compliant patients, there is a high chance of recurrent ulceration and symptoms due to failure to correct the underlying pathology.[2,3] Milic et al[4] found a 24% recurrence rate at 1 year in patients compliant with compression vs a 53% recurrence rate in those without ($P < .05$). This study buttresses the plethora of literature demonstrating that compression therapy decreases but does not prevent ulcer recurrence.[5-8] Owing to poor ulcer healing with compression alone, other treatment strategies aim to treat the mechanisms of venous incompetence and reduce venous hypertension.

Although open perforator ligation (Linton procedure)[9] and subfascial endoscopic perforator surgery[10,11] improve ulcer healing,[12,13] they are both associated with high morbidity. A paradigm shift toward ablative therapy has occurred, with increased technical success and fewer complications.[14]

Ultrasound-guided sclerotherapy (UGS) has recently been advocated to treat IPV associated with venous ulcers. Masuda et al[15] demonstrated good technical results with low complication rates using UGS for treatment of IPV. Although factors affecting overall venous ulcer healing and recurrence have been previously described,[2,5,16-19] published studies of specific modalities so far have focused primarily on improved subjective venous clinical scores

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rather than direct healing rates of venous ulcers. Without a randomized comparison between UGS and direct catheter-based ablation techniques, uncertainty persists regarding the best type of IPV treatment. In addition, limited data are available on the predictors of successful UGS of IPV and its impact on ulcer healing. The purpose of this report is to describe patient characteristics and periprocedural factors that affect rates of IPV closure using UGS and how this affects healing of venous ulcers.

METHODS

Institutional Review Board approval was obtained for prospective and retrospective reviews of a clinical database of patients with active venous ulcer(s) treated at the University of Pittsburgh Medical Center. Patients were identified from a prospectively maintained database of patients with venous ulcers and also through a query for ultrasound-guided injections in our electronic medical record system. Those with venous ulcers (CEAP 6, active ulcer)[20] who underwent UGS of IPV(s) from January 2010 to November 2012 were included in the analysis. All patients received standard of care compression and wound therapy throughout the study treatment period (Fig).

Initial evaluation. Patients underwent a complete history and physical and comprehensive venous duplex ultrasound assessment of surface varicosities as well as the deep, superficial, and perforator veins. All veins were assessed for dilation, reflux, presence of acute or chronic thrombus, and geographic relationship to the ulcer. Refluxing perforators of at least 3.5 mm in diameter and immediately next to the ulcer or directly feeding varicosities in the vicinity of the ulcer were considered pathologic. All patients were scored with CEAP classification.[20] Patients were assessed in this manner at the time of the initial presentation to the practice, but due to variations in practice patterns or patient preference, or both, patients may not have had treatment of perforator disease until it was demonstrated that compressive therapy alone was not successful in healing venous wounds.

Ulcer management. All patients underwent compressive therapy, usually with Unna boot(s) or short stretch bandages. Superficial debridement was performed on venous ulcers at the discretion of the provider. Patients with saphenous vein reflux of >1 second and a diameter ≥5 mm were treated with radiofrequency or laser ablation. Patients were included in the study if they had persistent ulceration and refluxing perforators >3.5 mm after saphenous ablation.

UGS technique. Before the injection, the location(s) of the perforator(s) were described in the ultrasound report, and this detailed documentation was used as a reference for follow-up comparison. UGS injections were performed by board-certified vascular surgeons with the aid of a registered vascular technologist using a Logiq 9 or E9 machine (General Electric Medical Systems, Milwaukee, Wisc). Foam was prepared using the Tessari method with a 4:1 air/sclerosant mixture.[21] Before May 2010, 1% sodium tetradecyl sulfate (STS) was used. After May 2010, 1% or 3% polidocanol sclerosing agent was used at the discretion of the provider.

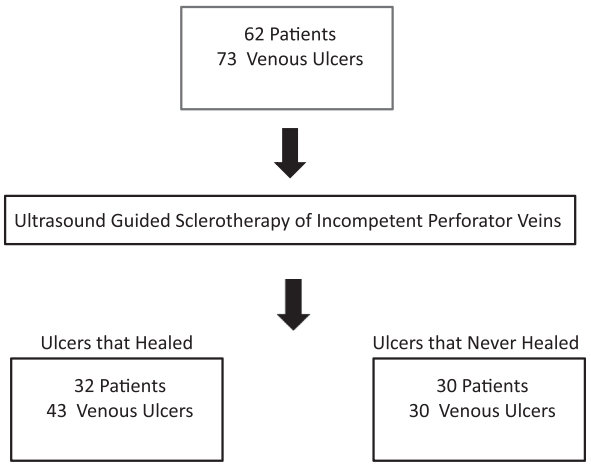

Fig. Study design.

Under direct ultrasound visualization, a 23-gauge needle was inserted into the varicosities fed by the IPV. Foam was prepared and immediately instilled into the cannulated vein under direct ultrasound visualization. The skin surrounding the ulcer and injection site was massaged to move the foam into the perforator as well as into adjacent varicosities or venous plexi. When foam sclerosant filled the IPV, pressure was held at the junction of the IPV and the deep vein for at least 2 minutes with an ultrasound probe. The injected perforating vein and surrounding varicosities were subsequently imaged to ensure sclerosis. A goal amount of ≤10 mL of foam was used per injection session to limit the amount of air instilled. Patients with multiple perforators could have several injections sessions scheduled to limit foam. After the injection, deep veins were imaged to ensure that they were clear of foam and compressible.

Patients were supine during the injection, compression was applied, and they were allowed to ambulate immediately after. Compression therapy was applied immediately after the procedure and left in place for at least 24 hours before the patient's standard wound care and compression therapy were resumed. For patients with Unna boots, the dressing was reapplied immediately after the UGS procedure. Patients receiving anticoagulation did not have this therapy held during the injections. All patients underwent an UGS injection in at least one IPV during the study period, and some had multiple injections in an IPV or multiple IPVs.

Follow-up. Patients with continuous Unna boot compression therapy were seen weekly after treatment according to the standard of clinical care. Patients receiving other wound care and compression therapies were seen at 2, 4, and 6 weeks and then every 6 weeks thereafter. At 2 weeks, a duplex ultrasound assessment by the same technologist used during the injection was performed to evaluate for thrombosis of the injected perforator, rule out deep vein thrombosis (DVT), and assess for new IPVs.

Repeat ultrasound imaging to assess for new perforators or recanalization of treated IPVs was performed for a decline or stagnation in the progress of wound healing or for other clinical indications.

Venous ulcer(s) were measured at each visit and recorded in a flow sheet imbedded in the electronic medical record. The area of the ulcer was calculated to determine the rate of healing. The dates of complete ulcer healing and last known follow-up were recorded for each patient. After complete ulcer healing, patients were told to continue compression and return for any new symptoms. Phone contact was initiated when patients were absent from the clinic for ≥6 months to ensure that no new ulcers had developed.

Outcomes and definitions. Primary outcomes included (1) incidence of thrombosis after UGSs of IPV(s), (2) success of complete closure of all IPVs in an ulcerated limb, and (3) healing status, a binary outcome defined by the presence or absence of a venous ulcer at last known follow-up. The secondary continuous outcome focused on ulcer recurrence, which was identified as ulcer healing and then opening in the same anatomic area at any point during the study period.

Statistical analysis. All statistical analysis was conducted by the Clinical and Translational Science Institute at the University of Pittsburgh Medical Center using R 2.15.1 software (R Foundation for Statistical Computing, Vienna, Austria) and Stata 11.2 software (StataCorp LP, College Station, Tex).

Analyses were initiated by running exploratory univariate models using clinically relevant variables. For each primary and secondary outcome, each demographic, comorbidity, and procedural predictor was entered by itself in a linear (for continuous outcomes) or binomial (for dichotomous outcomes) mixed-effects model, which accounts for the repeated measures of multiple ulcers in individual patients. The coefficient (continuous outcomes) or odds ratio (OR; dichotomous outcomes) was calculated with the P value of $< .05$ considered significant. Within each outcome, any variable that achieved $P < .20$ significance in univariate modeling was selected as a candidate for multivariable modeling. Multivariable modeling was conducted as a backward stepwise regression, excluding the least significant variable until only variables with $P < .10$ remained. Procedural predictors with partial collinearity with the outcome were not tested or included. Linear or binomial mixed-effects models were used to account for multiple ulcers from the same patient by means of incorporating a random effects term and robust standard errors.

RESULTS

Analysis of UGS injections of IPVs from January 2010 to November 2012 identified 73 venous ulcers in 62 patients who had compression and standard wound care for an average of 28 months before perforator ablation. Follow-up duplex ultrasound imaging was performed in 98% of patients. At the last follow-up visit, ulcers had healed in 32 of 62 patients (52%), whereas 30 patients had at least 1 nonhealed ulcer (Table I). Of 73 ulcers, 43 ulcers healed (group H), whereas 30 ulcers recurred or never healed (group NH), for a healing rate of 59% at the last follow-up. Mean initial ulcer size was 3.56 cm^2 in group H vs 15.15 cm^2 in group NH ($P = .10$). Median initial ulcer size was 1.61 cm^2 in group H vs 4.40 cm^2 in group NH.

Table I. Demographic variables in patients undergoing ultrasound-guided sclerotherapy (UGS) of incompetent perforator veins (IPV)

Variable	*Result (N = 62)*
Male, %	55
Mean age (range), years	57.1 (22-85)
BMI >30 kg/m^2, %	53
Deep venous reflux, %	31
Previous DVT, %	36
Smoking history, current smoking, %	53
Diabetes mellitus, %	13
Hypercoagulable state, %	5
Hyperlipidemia, %	47
Hypertension, %	71
Chronic obstructive pulmonary disease, %	5
Taking medication	
Aspirin, %	36
Coumadin,[a] %	21
Aspirin and Coumadin, %	8
Diuretic, %	39

BMI, Body mass index; *DVT,* deep vein thrombosis.
[a]Bristol-Myers Squibb, Princeton, NJ.

Perforator injection results. A total of 189 injections were performed. An average of 10.2 mL foam was used per session: 1% polidocanol used in 74% of injections, with 3% polidocanol used in 86% of these. There were no differences in STS 1% vs 1% or 3% polidocanol injection thrombosis rates or complications. The overall IPV closure rate was 54%. Thrombosis occurred in 69% of injections for group H vs 38% of the injections for group NH ($P < .001$). At the end of follow-up, 92% of group H ulcers had closure of all IPV in the affected limb (complete closure) vs 68% of group NH ulcers ($P = .02$). The average number of unsuccessful injections before the first successful injection was 0.28 for group H vs 0.52 for group NH ($P = .29$). Group H ulcers averaged 2.3 injections per ulcer vs 3.1 in group NH ($P = .13$).

After the first UGS, 48 ulcers had thrombosed IPVs and 25 ulcers had IPVs that failed to thrombose (66% closure rate for first injection). There were 116 subsequent UGS treatments of IPVs, 52 (45%) of which were successful ($P = .12$ compared with initial injections). In group H, 36 of 54 subsequent injections (67%) were successful, compared with group NH, where 16 of 62 subsequent injections (26%) were successful ($P < .001$). Of healed ulcers, 23% required a single perforator injection.

Postprocedure DVTs were seen in 3% of injections (six of 189) in six patients (10%), two in group H and four in group NH ($P = .35$). All were short-occlusion posterior

Table II. Univariate and multivariable binary logistic regression analysis to predict thrombosis of last ultrasound-guided sclerotherapy (*UGS*) injections of incompetent perforator veins (*IPVs*)

	Univariate			*Multivariable*		
Variable	*OR (per unit)*	*95% CI*	P	*OR (per unit)*	*95% CI*	P
Male sex	0.61	0.13-2.75	.52			
Age, years	0.98	0.93-1.03	.35			
Maximum BMI, kg/m^2	0.73	0.46-1.17	.20			
Maximum BMI >30 kg/m^2	0.27	0.05-1.36	.11			
Maximum weight, kg	0.96	0.91-1.01	.16			
Deep vein reflux	1.21	0.26-5.56	.80			
Previous DVT	0.98	0.23-4.24	.98			
Smoking history, current smoking	2.36	0.50-11.1	.28			
Hyperlipidemia	0.36	0.09-1.45	.15			
Hypertension	0.39	0.05-2.91	.36			
Taking Coumadin[a]	0.13	0.0003-55.6	.51			
DVT after UGS of IPV	0.06	0.0003-13.5	.31			
No. of UGS of IPV	0.65	0.48-0.87	.004	0.65	0.48-0.87	.004
Initial follow-up to last follow-up, days	1.0001	0.9995-1.00	.74			
Initial ulcer area, cm^2	1.02	0.95-1.08	.66			

CI, Confidence interval; *BMI,* body mass index; *DVT,* deep vein thrombosis; *OR,* odds ratio.
[a]Bristol-Myers Squibb, Princeton, NJ.

Table III. Univariate and multivariable linear regression analysis to predict percentage of thrombosis of ultrasound-guided sclerotherapy (*UGS*) injections of incompetent perforator veins (*IPVs*)

	Univariate			*Multivariable*		
Variable	*Net effect (per unit)*	*95% CI*	P	*Net effect (per unit)*	*95% CI*	P
Male sex	−0.18	−0.35 to −0.01	.04	−0.21	−0.37 to −0.02	.03
Age, years	−0.003	−0.009 to 0.004	.41			
Maximum BMI, kg/m^2	−0.01	−0.03 to −0.002	.01			
Maximum BMI >30, kg/m^2	−0.19	−0.36 to −0.03	.02			
Maximum weight, kg	−0.002	−0.003 to −0.0005	.01			
Deep vein reflux	−0.04	−0.23 to 0.14	.63			
Previous DVT	−0.08	−0.26 to 0.09	.35			
Smoking history, current smoking	0.10	−0.07 to 0.27	.26			
Hyperlipidemia	−0.09	−0.26 to 0.09	.33			
Hypertension	−0.10	−0.29 to 0.09	.30			
Taking Coumadin[a]	−0.18	−0.36 to 0.005	.06	−0.21	−0.38 to −0.05	.01
DVT after UGS of IPV	−0.22	−0.50 to 0.07	.14	−0.25	−0.53 to 0.02	.06
Initial follow-up to last follow-up, days	−0.00003	−0.0001 to 0.00005	.46			
Initial ulcer area, cm^2	−0.002	−0.005 to 0.002	.34			

CI, Confidence interval; *BMI,* body mass index; *DVT,* deep vein thrombosis.
[a]Bristol-Myers Squibb, Princeton, NJ.

tibial vein thromboses. In these patients, 33% were already taking warfarin for various reasons and the remaining 66% were prescribed 325 mg/d aspirin, with 100% recanalization of their short-occlusion thromboses on follow-up duplex ultrasound assessments. No other injection complications were seen.

Predictors of IPV thrombosis. Univariate analysis revealed an increased number of UGS injections negatively predicted successful thrombosis of IPVs (Tables II and III). For every additional UGS injection, we expect to see a 35% decrease in the odds of an eventual successful thrombosis of IPVs (OR, 0.65; 95% confidence interval [CI], 0.48-0.87; $P = .004$).

Increased weight ($P = .01$), increased body mass index (BMI; $P = .01$), BMI >30 kg/m^2 ($P = .02$), and male gender ($P = .04$) all negatively predicted thrombosis after UGS. Male gender highly correlated with increased BMI, and thus, gender association may be a result of men with increased BMI in our study population.

Multivariable modeling similarly demonstrated that postprocedural DVT ($P = .06$), male gender ($P = .03$), and warfarin use ($P = .01$) negatively predicted IPV thrombosis.

Predictors of ulcer healing and recurrence. Ulcer healing was predicted by IPV thrombosis (Tables IV and V). For each 10% increase in IPV thrombosis, we saw a 16%

Table IV. Univariate and multivariable binary logistic regression analysis to predict ultimate ulcer healing

	Univariate			*Multivariable*		
Variable	*OR (per unit)*	*95% CI*	P	*OR (per unit)*	*95% CI*	P
Male sex	0.64	0.25-1.64	.35			
Age, years	0.98	0.95-1.02	.36			
Maximum weight, kg	0.998	0.99-1.0	.63			
Deep vein reflux	1.07	0.40-2.87	.89			
Previous DVT	0.89	0.34-2.31	.81			
Smoking history, current smoking	1.31	0.52-3.35	.58			
Hyperlipidemia	0.75	0.29-1.92	.55			
Hypertension	0.88	0.30-2.63	.83			
Taking Coumadin[a]	0.96	0.36-2.60	.95			
DVT after UGS of IPV	0.32	0.05-1.86	.20			
Last UGS IPV injection a success	4.50	1.23-16.5	.02	4.87	1.28-18.47	.02
No. of UGS of IPV	0.82	0.65-1.03	.10			
Initial follow-up to last follow-up, days	1.0002	0.9996-1.0008	.46			
% Success UGS of IPV	4.31	1.06-17.96	.04			
Initial ulcer area, cm^2	0.92	0.84-1.01	.10	0.92	0.83-1.01	.08

BMI, Body mass index; *CI,* confidence interval; *DVT,* deep vein thrombosis; *IPV,* incompetent perforator veins; *OR,* odds ratio; *UGS,* ultrasound-guided sclerotherapy.
[a]Bristol-Myers Squibb, Princeton, NJ.

Table V. Univariate and multivariable linear regression analysis to predict ulcer recurrence

	Univariate			*Multivariable*		
Variable	*Net effect (per unit)*	*95% CI*	P	*Net effect (per unit)*	*95% CI*	P
Male gender	0.50	−0.15 to 1.15	.13			
Age, years	−0.02	−0.04 to 0.01	.14	−0.02	−0.34 to 0.0004	.05
Maximum weight, kg	0.003	−0.003 to 0.008	.34			
Deep vein reflux	0.45	−0.25 to 1.16	.21			
Previous DVT	−0.04	−0.73 to 0.65	.91			
Smoking history, current smoking	0.34	−0.31 to 1.002	.30			
Diabetes mellitus	0.90	−0.07 to 1.87	.07			
Hyperlipidemia	−0.002	−0.67 to 0.66	.99			
Hypertension	0.49	−0.24 to 1.21	.19	0.78	0.01 to 1.54	.04
Taking Coumadin[a]	0.37	−0.35 to 1.07	.31			
DVT after UGS of IPV	−0.66	−1.16 to 0.94	.84			
Last UGS IPV injection a success	−0.0003	−0.78 to 0.78	.999			
Initial follow-up to time to first UGS of IPV, days	0.0004	0.0001-0.001	.01			
No. of UGS of IPV	0.05	−0.09 to 0.18	.50			
Initial follow-up to last follow-up, days	0.0004	0.0001-0.0006	.005	0.0003	0.00005 to 0.0006	.02
% Success of UGS IPV	−0.58	−1.47 to 0.30	.19			
Initial ulcer area, cm^2	−0.004	−0.02 to 0.009	.54			

CI, Confidence interval; *DVT,* deep vein thrombosis; *IPV,* incompetent perforator veins; *UGS,* ultrasound-guided sclerotherapy.
[a]Bristol-Myers Squibb, Princeton, NJ.

increase in the odds of healed venous ulcer status at the end of follow-up (OR, 4.31; 95% CI, 1.04-17.95; $P = .04$). Patients with complete IPV closure (thrombosis of all perforating veins in a limb) on the last UGS had a 3.5-times greater chance of ulcer healing compared with failure of complete closure (OR, 4.50; 95% CI, 1.23-16.51; $P = .02$).

Multivariable modeling demonstrated IPV complete closure positively predicted ultimate ulcer healing (OR, 4.87; 95% CI, 1.28-18.5; $P = .02$), whereas each increase in cm^2 initial ulcer area negatively predicted ultimate ulcer healing (OR, 0.92; 95% CI, 0.83-1.0; $P = .08$). Increased age at the initial visit predicted fewer recurrences of ulcers in the multivariable model, whereas increased follow-up time and hypertension were seen with increased ulcer recurrence.

Variables that negatively influenced ulcer healing on univariate analysis included additional perforator injections (OR, 0.82; 95% CI, 0.65-1.03; $P = .1$) and increased initial ulcer size (OR, 0.92; 95% CI, 0.84-1.01; $P = .1$). Time from the initial visit to the first perforator injection appeared to predict recurrence of ulcers. Each year of ulcer existence before injection predicted 0.14 more recurrences of ulceration ($P = .01$). In addition, each additional year of

follow-up after injection predicted 0.14 ulcer recurrences ($P = .01$).

Follow-up. Overall median follow-up with interquartile range (IQR, 25th-75th percentile) was 33.5 months (IQR, 8.9-79.9 months), and median follow-up for patients in various healing groups broke down as healed ulcers, 12.2 months (IQR, 5.7-38.6 months); recurrent ulcers that were healed at last follow-up, 94.7 months (IQR, 60.3-103.0 months); ulcers that healed, recurred, and were open at last follow-up, 71.0 months (IQR, 33.6-93.9 months); and ulcers that never healed, 18.1 months (IQR, 6.1-44.7 months). We grouped the two recurrent ulcer groups in comparison with ulcers that healed without recurrence or never healed in a mixed-effects model, which demonstrated that total follow-up time was strongly associated with recurrence. Each additional year of follow-up was associated with a 56% increase in chance of recurrence ($P = .001$). Other factors that were associated with ulcer recurrence were younger patient age ($P = .05$) and hypertension ($P = .04$).

Because follow-up time strongly predicted recurrence, healing status is likely influenced by how long the patients' ulcers were monitored and reflects fluidity in the healing of this population. A multivariable logistic regression was run on 62 ulcers in 62 patients, comparing never-healed ulcers with those ulcers that healed and recurred in an effort to ascertain if there were factors that appeared to prohibit ulcer healing at any time point. Predictors of increased ulcer healing were closure of IPVs ($P = .04$) and follow-up ($P = .09$). If recurrent ulcers were analyzed separately from healed ulcers, multivariable logistic regression analysis revealed diuretic use ($P = .07$), more UGS IPV injections ($P = .08$), and longer follow-up time ($P = .01$) were associated with recurrence.

DISCUSSION

Despite the proven efficacy of compression therapy,[5,6,22-26] venous ulcers will not heal in a subset of compression-treated patients despite strict compliance. Correction of great saphenous vein reflux is associated with significant ulcer healing and decreases in ulcer recurrence.[25] For ulcers that persist, minimally invasive elimination of pathologic IPVs near the ulcer increases healing rates and may decrease recurrence, with few wound complications and high rates of technical success.[10,14,27] Patients with healed ulcers that were treated with IPV ablation and continued to maintain compression therapy had significantly reduced recurrence rates compared with compression alone.[28] However, perforator ablation requires instrumentation into or near an active ulcer, is a more difficult technique to master, and does not treat the associated varicosities fed by an IPV.

Thermal ablation of perforators has a high overall technical closure rate (~80%-90%).[29-31] Early results of sclerotherapy by Guex[32] showed a comparable 90% occlusion rate after three or fewer sessions. Ultrasound-guided perforator injection is attractive because this therapy can be delivered through a varicosity remote from the ulcer and thus decreases wound complications and procedural discomfort. In addition, this therapy can be used to eliminate multiple pathologic perforators and their associated varicosities in one sitting. It is rapidly performed and is technically straightforward. Unlike ablative techniques, sclerotherapy is able to be performed virtually 100% of the time. Many series of ablative perforator techniques appear to report closure rates for perforators successfully cannulated but not all attempts at cannulation and ablation. In addition, UGS is much less expensive and could potentially represent significant savings to the health system. Previous studies of UGS have demonstrated thrombosis rates after 3 months varying from 69% to 96%, whereas follow-up studies at 1 to 2 years demonstrated rates of 53% to 80% in great saphenous veins and varicose veins.[33] However, little work has been done to illustrate the effect of UGS on ulcer healing when performed on patients without other treatable venous pathologies.

Our study population consisted of patients in whom compression therapy had failed for more than 2 years before treatment and who had no superficial reflux. In this very difficult population, perforator thrombosis was achieved in 54% of injections, demonstrating the complexity and severity of venous disease as well as a major drawback of this technique. Physiologic reasons for a decrease in successful IPV thrombosis compared with axial veins includes that IPVs are short high-flow vessels, multiple perforators may feed a network of varicosities, and many patients (>30%) are receiving chronic anticoagulation. Previous work has demonstrated decreased thrombosis after UGS in patients with ulcer.[15] We found warfarin use resulted in a 20% decrease in thrombosis.

Each ulcer averaged 2.67 injections. Repeated injections were performed for incomplete thrombosis after the initial injection, recanalized perforators, and treatment of new or additional perforators. Each additional injection predicted 35% lower odds of the eventual total IPV thrombosis after UGS. This likely reflects two potentially overlapping populations: patients with many perforators in the ulcerated limb who required several sessions to safely treat these veins and patients who had a lower rate of perforator thrombosis. Regardless, both groups represent more severe venous and perforator disease. We found that repeated treatments had a success rate of 45%. Although this was lower than the initial injection thrombosis rate of 66% ($P = .12$), ulcer healing increased with successful thrombosis of IPVs. Thus, we endorse continued perforator injection or other methods of perforator ablation in the face of initial failure until thrombosis is achieved, because this was the most significant predictor of ulcer healing.

UGS of IPVs is a safe treatment, with few complications and an easy ability to retreat in the setting of initial failure of thrombosis. After polidocanol was approved by the Food and Drug Administration as a sclerosant, we changed from STS due to evidence indicating polidocanol may have a better safety protocol, be as or more effective than STS, and be better tolerated.[34] Our incidence of DVT was low and comparable with other known

studies.[15,35-37] The most common side effects of perforator ablation include ecchymosis, induration, and pain, whereas paresthesias, hyperpigmentation, and phlebitis occur in the minority of patients.[27,38,39] Multiple needle punctures during sclerotherapy can lead to vasospasm or hematoma, but in our population, the common side effects seen during sclerotherapy were minimal. Patients tolerated sclerotherapy much more comfortably than ablation therapy and often recovered faster.[40,41] Thrombosis of IPVs was the most powerful predictor of venous ulcer healing, and ulcer healing was achieved in >50% of patients. These patients had suffered with venous stasis wound(s) for years and had few remaining therapeutic options. A large initial ulcer area, however, predictably demonstrated a lower chance that an ulcer would ultimately heal, even with successful perforator thrombosis.

Healing status of ulcers was determined at an arbitrarily defined study end period, and thus, recurrence of venous ulcers incorporates the time-dependent nature of the disease. Our data demonstrate recurrence of ulcers was significantly predicted by length of follow-up, a finding that is consistent with the natural history of venous ulceration and represents a selection bias, in that patients who heal are less likely to return to the clinic, even when prompted.[42] Increased ulceration with long-term follow-up also speaks to the nature of new IPVs appearing in the at-risk areas or the occurrence of late recanalizations. Unfortunately, our largely retrospective review did not provide adequate data on the exact perforator locations to enable accurate reporting of whether new injections a significant time after demonstrated thrombosis represented de novo perforators vs recanalization. We did find that continued therapy and repeat injections with IPV thrombosis led to healing. Thus, improving comorbidities, such as hypertension, continued use of compressive therapy, and aggressive surveillance and perforator ablation may all contribute to maintenance of ulcer healing.

This study has a number of limitations. The most important is the largely retrospective nature of the review. Variances in long-term follow-up have prohibited standardized healing curves. Our small sample size, combined with high variance in initial ulcer sizes and heterogeneity in recurrence rates, precluded a cumulative analysis of healing rates of all ulcers.

Owing to the inconsistency of quality of life data being collected on patients, it was not valuable in our current analysis. Similarly, it was not possible to control for wound care methods. Ointments and exact methods of compression, for example, Unna boot vs short stretch bandages, often changed according to patient preferences, ability to comply with the prescribed regimen, and perceived success of the current therapy. In addition, although detailed documentation of perforator location was recorded during initial ultrasound evaluation and foam injection, variability in ultrasound sonographers may make follow-up comparison difficult in determining whether a suspected perforator recurrence was newly formed or indeed recanalized.

CONCLUSIONS

Ultrasound-guided injection of refluxing perforator veins in CEAP 6 patients was found to be safe and to predict ulcer healing. Thrombosis of pathologic perforators was the most powerful predictor of ulcer healing in our analysis. Perforator closure may require multiple injections but is associated with low complication rates. Foam sclerotherapy, or other methods of perforator closure, is therefore recommended for treatment of nonhealing venous ulcers.

AUTHOR CONTRIBUTIONS

Conception and design: MK, EH, ED
Analysis and interpretation: MK, EH, ED
Data collection: MK, EH, ED
Writing the article: MK, EH, DW, RC, SH, ED
Critical revision of the article: MK, ED
Final approval of the article: MK, ED
Statistical analysis: MK, DW, ED
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Overall responsibility: ED

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DISCUSSION

Dr Albeir Mousa (*Charleston, WVa*). I have two questions. The first, what size perforator you have treated, and how far from the ulcer location that can still contribute ulcer pathology?

Dr Ellen Dillavou. We follow the Society for Vascular Surgery (SVS) guidelines for pathologic perforators; so, a perforator of ≥3.5 mm is considered pathologic and so we will inject anything of that size or larger.

Dr Mousa. So about two-thirds of your cohort was resistant to treatment. And I notice you keep following them. Did you evaluate the central venous system, iliac vein, like any venous outflow study to delineate this issue?

Dr Dillavou. Yes, we perform complete duplexes of all of our patients initially and then as clinically indicated. So, if we performed our intervention and the ulcer heals, we continue that course. However, if there is a stagnation in healing, we go back and perform a new duplex ultrasound. If there is any suggestion of venous outflow obstruction, such as with chronic DVT or dampened femoral waveforms on ultrasound, we would then perform a central venous study.

Dr Nicos Labropoulos (*Stony Brook, NY*). That was a great talk. I think this is real-world data, and this is what you expect to see in the population you are presenting. However, it is a bit misleading to indicate that the treatment of the perforators by the foam is what is causing the ulcers to heal. I believe that the foam does the job by closing all the refluxing tributaries and particularly the microvascular tree, which is actually responsible for the development of the ulcer. And in your population in particular it is evident, because only one-third of your patients had deep vein

disease. So it is clear that the foam was successful to that extent because you were able to treat a significant number of veins within and around the ulcer.

Dr Dillavou. I completely agree, and one advantage of foam is that it does treat the network of varicosities. I think this is one tool. Dr Lawrence has elegantly demonstrated that ablation of perforators also increases ulcer healing, so the foam perforator ablation has value. This is just one part of the ulcer treatment package.

Dr Kathleen Gibson (*Bellevue, Wash*). The question I had, and I might have missed in your talk, what was your compression regimen after treatment? Did you track patient compliance? And if so, did that have any effect on either ulcer healing or the success of thrombosis of the perforator, or do you think that that is an important piece in the healing and in the success of your procedure?

Dr Dillavou. Our standard regimen is to put patients in a compressive stretch wrap for 24 hours after foam sclerotherapy. Or if they are in an Unna boot, we put the Unna boot on immediately after the treatment and leave that on for 3 days, or a week, however long the patient leaves the Unna boot on.

I do think it is important, and in general our patient population was very compliant with compression. Unfortunately, the largely retrospective nature of this study didn't allow us to control for each type of compression, and there was a lot of bouncing back and forth with patients between different types of Unna boots and short stretch bandages, et cetera. But they were all in high-grade compression. We are very aggressive with that and, by and large, the patients are compliant.

Dr Gregory Moneta (*Portland, Ore*). I have a question about the status of the patients prior to when you began treating them. You said that they were all under maximum medical management. Were these patients de novo patients when they presented to you? If not, and if they were under your continuous management, why do you wait 2 years to treat them?

Dr Dillavou. We get a large number of patients referred from other institutions. And the reason it was only 2 years of compressive therapy prior to intervention for many patients is because although they would report a history of many years of ulcer, they were not under our care at that time. And so we started tracking the study from when we knew they were getting adequate compression and medical therapy. Much of the medical and compressive therapy was done in our clinics.

This study also reflects a change in our practice patterns: becoming more aggressive with elimination of refluxing perforators and correction of outflow obstruction, and that has happened over the last few years. Prior to the mid-2000s we were less aggressive in our practice and had a large number of patients who were treated with compression only.

Dr Alan Dietzek (*Danbury, Conn*). I was curious, how did you select your sclerosant regimen for these patients? Do you use a higher concentration if you don't get a thrombosis of the perforator the first time? Did you see a difference when you switched to polidocanol from Sotradecol (AngioDynamics, Latham, NY)? And have you considered the combined use of foam sclerotherapy and heat ablation for those perforators that don't thrombose with sclerotherapy only?

Dr Dillavou. We switched from Sotradecol to polidocanol as a group. We made a total change in our practice in May 2010 because we felt that polidocanol was safer and better tolerated than Sotradecol. We did not see a difference in thrombosis rates or complications between Sotradecol and polidocanol. Initially we were using 3% polidocanol for all ultrasound-guided perforator injections because we felt that that would be more effective. But then after the Varisolve trial (BTG International Inc, West Conshohocken, Pa) results showed that there was not a significant difference between 1% and 3%, we then downgraded to 1% and we have not seen a difference in our thrombosis rates or complications. And so now 1% polidocanol is the standard that we use.

Based on these results, we have become more aggressive with heat ablation of perforators. So anyone with a 5-mm perforator, the obese men on Coumadin (Bristol-Myers Squibb, Princeton, NJ), and those who fail ultrasound-guided injection, all get a heat ablation, and those we are doing as a combined heat ablation and chemical ablation at the same time hopefully through the same access site.