Endovenous Radiofrequency Ablation (Venefit Procedure): Impact of Different Energy Rates on Great Saphenous Vein Shrinkage

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Background: Despite adequate treatment of varicose veins, recurrences and primary failures still occur. This article hypothesizes that increasing the dose of radiofrequency ablation (RFA) could improve efficacy through inducing a greater shrinkage of the treated vein.

Methods: A comparative clinical study of 67 extremities with varicose veins caused by great saphenous vein (GSV) reflux treated with RFA ClosureFAST was conducted. Group 1 ($n = 22$) received 1 treatment cycle (20 sec) and group 2 ($n = 45$) received 2 cycles (40 sec) along the GSV trunk. Clinical and duplex follow-up were performed at day 4, and at 1, 3, and 6 months. The main outcomes measured were GSV diameters, occlusion rate, and secondary effects. Statistical analysis was performed using the Student's t test, linear mixed model, Bland-Altman plot, Lin's concordance correlation coefficient, and intraclass correlation coefficient.

Results: Both groups were comparable for demographic and specific study variables with a very low intraobserver variability. The immediate occlusion rate was 100% for both groups. Group 2 showed a quicker and greater reduction in medium diameter along the period of the study ($P = 0.0074$). Beyond the 6-month period of study, 1 partial GSV recanalization in group 1 and 1 complete GSV recanalization in an obese patient in group 2 were detected. No skin burns, paresthesia, or deep vein thromboses appeared.

Conclusions: Two cycles of RFA treatment in all segments of the GSV achieves quicker and greater vein shrinkage of the medium diameter without an increase in side effects. Further studies are needed to evaluate the implications in terms of intermediate and long-term clinical efficacy.

INTRODUCTION

Over the past decade, technologic advances have allowed for the development and application of new minimally invasive therapeutic options for the treatment of truncal varicose veins, such as endovenous radiofrequency ablation (RFA). The aim of these techniques is to reduce the disadvantages associated with conventional surgery and increase efficacy when possible. The Closure procedure using radiofrequency was first performed in a clinical setting in 1998 and obtained approval from the U.S. Food and Drug Administration (FDA) in March 1999. After several modifications of the original Closure design, a new-generation RFA platform (ClosureFAST™; VNUS Medical Technologies, Sunnyvale, CA, USA) received FDA approval in May 2006. ClosureFAST has been on the market since 2007, with many subsequent procedures performed.

The therapeutic objective of RFA is to induce a fibrotic occlusion of the varicose vein with subsequent atrophy and disappearance.[1,2] From a physics point of view, endovenous RFA is based on the

transference of thermal energy to induce a modification of the vein wall structure and on the transformation of electromagnetic radiation into thermal energy. This locally generated heat induces microscopic and macroscopic changes in the treated vein wall. The most important of these changes is the denaturalization of the molecular structure of collagen, which in turn leads to a significant increase in contractile force. This increased contractile force translates into a major reduction of the vein lumen through the shortening and thickening of the wall.

Some studies on endovenous laser treatment have shown a relationship between the thermal energy transferred and the effectiveness of the procedure.[3,4] This specific aspect, however, has been insufficiently studied with respect to ClosureFAST radiofrequency energy.

The goal of this study is to determine whether an increase of the energy supplied allows for greater tissue ablation and therefore could to improve clinical efficacy.

METHODS

Patients and Study Design

The authors conducted a comparative nonrandomized cohort study of 67 concurrent extremities treated with VNUS ClosureFAST radiofrequency energy using patients in their database. The authors began using RFA in January 2006, and have since treated 225 patients with this modality. The population selected for the study consisted of 67 extremities in 59 concurrent patients with varicose veins secondary to great saphenous vein (GSV) reflux treated with ClosureFAST between May 2007–February 2010, with prospective data collection and disposable specific follow-up data. Based on the possibility of safely applying more than 1 cycle at the GSV trunk according to manufacturer instructions, we applied 2 cycles along the GSV systematically in the last 45 extremities. We decide to evaluate the efficacy of their daily practice with this modification of the standard protocol.

The objective of this study was to know the effects of 2 different energy doses on GSV obliteration. Anamnesis and physical examination were performed to document varicosities, and patients were categorized according to CEAP clinical class. Exclusion criteria were recurrences, arterial insufficiency, previous deep vein thrombosis, pregnancy, and inability to ambulate. All patients gave informed consent for the procedure.

The authors supplied 2 different doses of energy along the GSV: group 1 (*n* = 22) received the standard treatment protocol: 2 cycles near the saphenofemoral junction (SFJ) and 1 treatment cycle (20 sec) along the rest of saphenous trunk. The catheter was immediately withdrawn after each segment had been treated to allow for further vein wall contraction. Group 2 (*n* = 45) received 2 cycles (40 sec) per 7-cm segment along the entire treated GSV. In both groups, vascular surgeon performed repeat catheter withdrawal, external compression with the probe, and treatment until the hatched area of the catheter was seen.

All patients underwent duplex ultrasound scanning (DUS) using the SonoSite MicroMaxx® ultrasound system (SonoSite, Inc, Bothell, WA, USA). The ultrasound criterion used to define reflux was reverse flow in the GSV lasting longer than 0.5 sec in the standing position after distal compression and release of the Valsalva maneuver.[5] Occluded veins were defined as those with no evidence of flow. Recanalization (with or without reflux) was defined as the documentation of flow in a previously occluded vein.

Technique

At the time of the procedure, all patients underwent another preoperative DUS in a standing position so that a venous mapping could be drawn with a skin marker. The trajectory of the vein and its depth, different diameters, ectasies, aneurysmal segments, and incompetent perforators and tributaries were drawn. The best place for the vein approach was also marked, frequently below the knee in the proximal third of the leg, so that the GSV was usually treated from the knee to the SFJ. The vein approach was obtained through percutaneous access using the Seldinger technique, or through a small cutdown if phlebectomy at the vein entry level was necessary. Tumescent anesthesia was injected into the saphenous compartment to protect the skin. The volume solution infiltrated was 10 mL per centimeter of vein to be treated. Most of the procedures were performed under local tumescent anesthesia with light intravenous sedation. The authors just used regional anesthesia in addition to the tumescent infiltration in patients who required a very extensive phlebectomy for a large number of varicosities or when a bilateral one-step procedure was performed.

RFA is a well-established technique. After the procedure, the success of the ablation was assessed in all patients with a DUS to confirm wall thickening, occlusion of the GSV, and patency of the

common femoral vein. All patients underwent concomitant microphlebectomy according to the Müller technique and ligature of incompetent perforators as part of the same procedure. Patients wore elastic bandages for 24 hours, followed by graduated above-the-knee class 2 compression stockings (20–30 mm Hg) (Medi, Bayreuth, Germany) for 5 days. After the operation, patients were encouraged to move around and walk without restriction. Routine prophylactic low-molecular-weight heparin was administered for 6 days according to the authors' personal varicose vein surgery protocol. Nonsteroidal anti-inflammatory drugs were recommended as merited by patient criteria.

RFA Generator and Catheter

The RFA procedure was performed using VNUS ClosureFAST. The heating element at the tip of this catheter measures 7 in diameter and 7 cm in length. The shaft of the catheter has markers spaced 6.5 cm apart. A thermocouple is located 1 cm from the proximal end of the heating element. The normal operating power range of the radiofrequency generator varies between 15 and 40 W during the 20-sec treatment cycle, with default settings for temperature and maximum power of 120°C and 40 W, respectively. The radiofrequency generator will automatically terminate energy delivery at the end of the 20-sec cycle. Power, which will initially increase as high as 40 watts, later decreases to 15–20 W after the first 10 sec of treatment.

Diameter Measurements

Vein diameters were always measured with the patient in standing position, because the authors think that represents the real vein inner surface that must be treated is important to take into account. Furthermore, this measurement represents the diameter exposed to gravitational forces. Because the GSV is not cylindrical, to avoid bias the authors selected 3 different measures: maximum, medium, and minimum diameters (D_{max}, D_{med}, and D_{min}, respectively). Nine determinations along the GSV (3 measurements for each maximum, medium, and minimum diameter reading) were obtained in each DUS examination, using the mean values for each. When the area of the vein was elliptical, the mean value between the long and short axes was used. A total of 3015 measurements were performed during the study period, and all measurements were recorded in Excel 11.0. A single vascular surgeon performed the DUS explorations and took the measurements. The DUS was performed using a SonoSite MicroMaxx (SonoSite, Inc.) apparatus with an HFL38/13-6 MHz multifrequency linear transducer.

Follow-Up

Patients were reexamined on the fourth day; at 1 week, 1 month, and 6 months; and yearly thereafter. Each visit included a clinical examination during which patients were asked about their symptoms, postoperative pain, and paresthesia, while staff recorded the presence of ecchymosis, hematoma, phlebitis (induration and erythema along the vein), or infection. A concomitant DUS examination was performed to check the GSV stump, occlusion in the treated vein, and its maximum, medium, and minimum diameters.

Statistical Analysis

Each baseline characteristic (age, sex, side [left leg or right leg], weight, body mass index [BMI]) was described and a comparison performed (χ^2 and Wilcoxon rank sum test). CEAP classification of class 4 or higher was 22% for group 1 and 33% for group 2. Differences among groups were analyzed using the Fisher's exact test. A P value of less than 0.05 was considered significant. The lineal mixed model of repeated mesures was used for the analysis of the specific study variables—the GSV diameters in the preoperative stage and during each DUS follow-up. To analyze intraobserver variability, the authors used the Bland-Altman plot, Lin's concordance correlation coefficient (Lin's), and the intraclass correlation coefficient (ICC).

RESULTS

Baseline Characteristics and Intraobserver Variability

A single surgeon performed RFA ClosureFAST on 67 GSVs in 59 concurrent patients. Seven patients received bilateral treatment (3 concomitantly and 4 in stages). The demographic characteristics (age, sex distribution, pathologic side) and preoperative different diameters of the GSVs were comparable for both groups. BMI was 25 ± 4 and 24 ± 4, respectively (P = not significant). No differences were seen in the median length of the vein being treated (group 1: 31 ± 7 cm; range, 14–45 cm, and group 2: 30 ± 8 cm; range, 14–45 cm). Patient stump length was also comparable (group 1: 13.9 ± 7.7 mm; range, 0–30 mm, and group 2: 13.7 ± 5.0; range, 5–30 mm). Among the patients, 71.5%

Table I. Patient demographic and anatomic characteristics

Variables	Group 1 (1 Cycle) ($n = 22$)	Group 2 (2 Cycles) ($n = 45$)	P value
Patients	21	38	
Age (SD) (years)	54 ± 15	55 ± 18	NS[b,c]
Age (range)	(31−80)	(18−83)	
Sex (M/F)	5/16 (24/76%)	7/31 (18/82%)	NS[a]
Mean weight (range) (kg)	71 ± 10 (57−94)	65 ± 12 (46−90)	NS[c,d]
Median weight (kg)	68	64	NS[c,d]
Mean height (range)	168 ± 7 cm (155−180 cm)	167 ± 10 cm (149−190 cm)	NS[c,d]
Median height	168 cm	167 cm	NS[c,d]
Mean BMI (range)	25 (22−39)	24 (17−37)	NS[c,d]
Median BMI	24	23	NS[c,d]
Side (R/L)	9/13% (41/59%)	24/21% (53/47%)	NS[e]
Mean maximum preoperative diameter	9.6 ± 3.4 mm	9.5 ± 3.0 mm	NS[e]
Maximum (range)	(4.5−18.0)	(4.5−19)	NS[e]
Mean medium preoperative diameter	6.7 ± 1.7 mm	6.8 ± 1.6 mm	NS[e]
Medium (range)	(4.1−10)	(3.5−11)	NS[e]
Mean length of treated segment	31 ± 5.4 cm	30 ± 7.0 cm	NS[e]
Distance from the SFJ	14 ± 5.9 mm	14 ± 4.2 mm	NS[e]

BMI, body mass index; F, female; L, left; M, male; NS, not significant; R, right; SD, standard deviation; SFJ, saphenofemoral junction.
[a]Mann-Whitney *U*-test.
[b]Wilcoxon 2-sample test.
[c]Fisher's exact test.
[d]Wilcoxon rank sum test.
[e]χ^2 test.

were treated under intravenous sedation and local tumescence (81% in group 1 and 62% in group 2). The amount of tumescent anesthesia (10 mL/cm) was similar for both groups. The rest of patients were treated under regional anesthesia. Three patients in group 2 received bilateral treatment in one session. The results of the study population are summarized in Table I.

The analysis of intraobserver variability showed excellent results, with high repeatability for the maximum (0.967 Lin's and 0.970 CCI) and medium (0.957 Lin's and 0961 CCI) GSV diameters. The minimum diameter measurements showed moderate (Lin's) or weak correlation (CCI) because of higher variability, and therefore the authors decided to reject them for the study analysis.

D_{max}

In the overall study population, a progressive shrinkage of the maximum diameter (D_{max}) was observed. Overall, absolute D_{max} decreased from 9.6 ± 3.2 mm (range, 4.5−19 mm) at basal to 4.7 ± 1.6 mm (range, 2.4−8.0 mm) at 6 months ($P < 0.0001$), representing a shrinkage rate of 53.5%. The reduction rate in the D_{max} for each group is shown in Table II.

Besides the absolute values, the authors studied the difference in basal values over time, and observed that half of the patients presented with a median reduction of 5.0 mm respective to their preoperative diameter. When the results were analyzed for each group, the authors observed that group 2 (two cycles along the entire GSV) always presented with a lower diameter than group 1 (single energy dose), with statistical significance seen on the fourth postoperative day ($P = 0.01$) (Fig. 1).

D_{med}

Throughout the study period, an evident reduction in the medium diameter (D_{med}) was seen. Overall, the mean absolute reduction in D_{med} at 6 months was 5.3 ± 1.8 mm (range, 1.1−7.8 mm), representing a reduction rate of 76.5%. The reduction rate of the D_{med} for each group is shown in Table III.

When the differences between both cohorts over the entire period studied were analyzed using the Student's *t*-test, group 2 showed a greater statistically significant reduction in D_{med} ($P = 0.0074$) (Fig. 2). When the results were analyzed using the linear model of repeated measures, statistically significant differences were observed on day 4, with group 2 showing a reduction of 1.01 mm more compared with group 1 ($P = 0.0139$; IC, 1.81−0.21). At 1 month, group 2 showed an

Table II. Maximum GSV diameter (D_{max})[a]

Variable	Group 1 (1 Cycle)		Group 2 (2 Cycles)		P value
	Diameter (mm)	Reduction rate	Diameter (mm)	Reduction rate	
Basal	9.6		9.5		
4th day	9.0	6%	7.3	23%	0[1]
1 month	7.2	25%	6.7	30%	NS
3 month	5.9	39%	5.7	40%	NS
6 month	5.3	44%	4.3	54%	NS

NS, not significant.

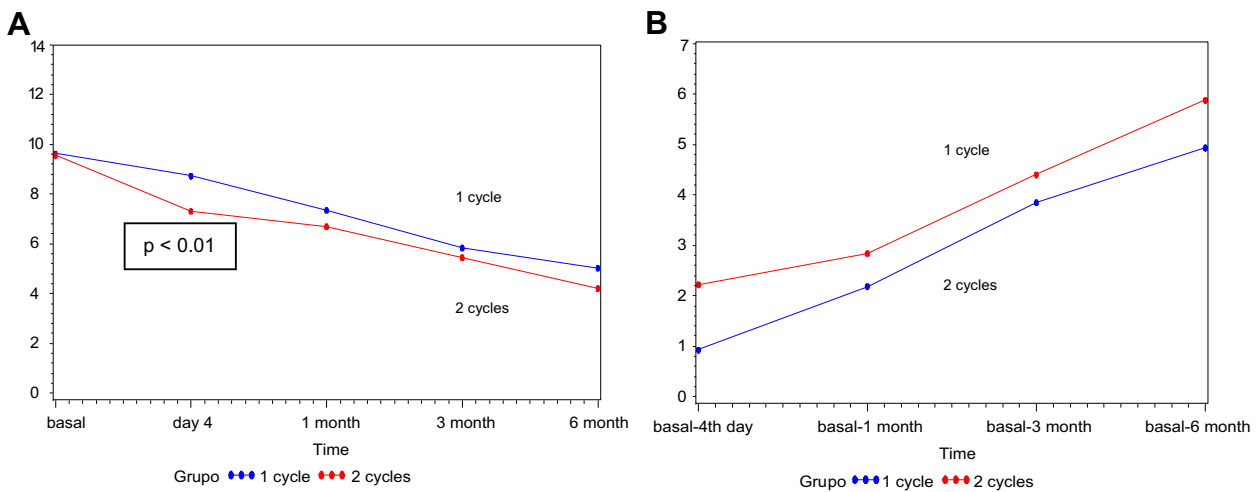[a]Reduction rate according to the time and group from basal.

Fig. 1. D_{max} for both groups at follow-up. (**A**) Absolute values (mm). (**B**) Differences from basal values (mm).

Table III. Medium GSV diameter (D_{med})[a]

Variable	Group 1 (1 Cycle)		Group 2 (2 Cycles)		P value
	Diameter (mm)	Reduction rate	Diameter (mm)	Reduction rate	
Basal	6.7		6.8		
4th day	5.4	20%	4.6	32%	0.013
1 month	5.2	22%	4.0	40%	0
3 month	4.0	40%	3.2	53%	NS
6 month	2.5	62%	1.1	83%	NS

NS, not significant.

[a]Reduction rate according to the time and group from basal.

average reduction of 1.29 mm relative to group 1 ($P = 0.0007$; IC, 2.02−0.57).

Follow-Up

The DUS examinations showed GSV occlusion and an absence of retrograde flow in all patients on completion of the procedure. The occlusion rate at 6 months was also 100% for both groups. Later on

the 6-month period of study, 1 patient in group 1 presented partial GSV recanalization alongside developed de novo anterior saphenous varicosity. At 12 months after the intervention, another patient with complete occlusion of the GSV also presented with de novo varicosity across the anterior saphenous vein that required treatment. One obese patient in group 2 showed complete GSV recanalization at 9 months. In the overall series, the rate of
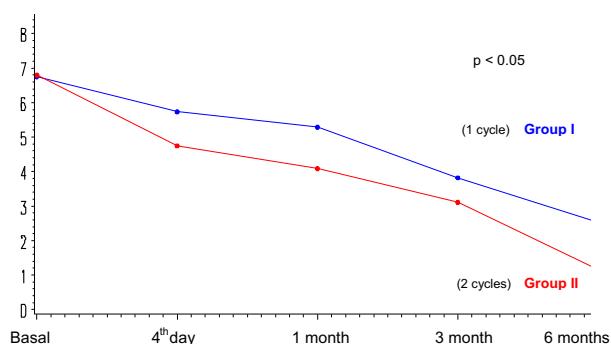
Fig. 2. GSV D_{med} reduction over the study period (t test and linear mixed model; $P < 0.05$).

recurrent varicosities is low, but in most cases it was linked to the potential for reflux into the anterolateral thigh tributaries, similar to that described in another paper.[6]

Complications

Despite the higher energy supplied, no skin burns, saphenous nerve–related paresthesia, or deep vein thrombosis occurred. In each group, 1 patient experienced a very light transient erythema and localized tenderness in the area with large GSV ectasias close to the condyle. Also in each group, 1 patient showed class 1 endovenous heat-induced thrombosis (EHIT) according to the Kabnick classification that regressed spontaneously in 1 week. No inguinal neovascularization was observed, with a median follow-up for both groups of 151 ± 173 days (maximum, 996 days).

DISCUSSION

RFA is a modern endovascular procedure to eliminate reflux in the saphenous veins. The good results reported in the literature[6,7,8,9,10] in addition to its minimally invasive character, ensure a promising role for this technique in the varicose vein therapeutic arsenal.[11] The complications occurring in its early years of use, such as skin burns, have clearly been overcome through appropriate patient selection and the use of tumescent anesthesia, and are becoming nonexistent.[12]

RFA is based on the transference of thermal energy; therefore, a sufficient amount of energy must be delivered to produce irreversible damage in the vein wall.[13] In endovenous thermal procedures, the amount of supplied energy per unit of area or per unit of length can be expressed in 2 ways: (1) linear endovenous energy density (LEED; expressed in J/cm) and (2) endovenous

fluence equivalent (EFE; expressed in J/cm^2),[3] which represents an approximation of the inner vein surface. The RFA generator delivers half of the energy in the first 8 sec to reach a therapeutic temperature of 120°C. The power delivered by the generator is variable during the treatment cycle to maintain a constant temperature. With a second treatment cycle at the same place, the energy delivered by the heating element is somewhat lower because the temperature is reached early.

The exact measurement of the energy delivered is difficult to determine under clinical conditions; however, this information was available based on previous reports.[7,14] Proebstle et al.[7] analyzed the amount of energy delivered with ClosureFAST in 63 patients following the standard protocol. The average LEED delivered was 116.2 ± 11.6 J/cm along the proximal segment and 68.2 ± 17.5 J/cm along the remainder of the vein, with an EFE at the proximal segment of 82 ± 25 J/cm^2. Lebard et al.[8] also studied the amount of energy in segmental RFA and found with similar results: an average LEED of 109 J/cm on the proximal segment and 59 J/cm on the rest of truncular segments, with an EFE of 30 J/cm^2 (range, 20–49). Although is not the same procedure, studies using endovenous laser have shown that more than 80 J/cm were needed to obtain successful results, suggesting a threshold LEED of 6.3 J/cm per each millimeter of vein diameter (veins with 10 mm diameter will need 63 J/cm).[3]

It is well known that some initial failures and late recanalizations have occurred several months after RFA.[3,15] This result may be from insufficient energy transference to the vein wall, and therefore higher energy doses could potentially improve efficacy. The standard RFA energy dose protocol is an adequate approach for most GSVs approximately 9 to 10 mm in diameter, but larger veins may require more joules. In a retrospective study, Calcagno[16] reported high efficacy in terms of closure rate (96%) for veins larger than 12 mm, but he did not specifically study the diameter changes over time.

Increasing the amount of energy supplied could accelerate the shrinkage time. Furthermore, it is well known that shrinkage in large veins is more difficult to achieve, and atrophy will take more time than in small veins. Given that when a vein is not yet atrophic the possibility of recanalization still exists, a shortening of this time could improve the therapeutic efficiency of RFA. This issue, however, has been insufficiently studied with ClosureFAST.

In this comparative analysis we treated 2 groups of patients who were comparable in demographic

characteristics and all anatomic (different diameters) and procedure-related variables (length of the vein treated, length of the SFJ stump). The main outcome was the vein diameter changes over time. Different diameters (D_{max}, D_{med}, D_{min}) were measured 3 times so that the mean values of each one could be used. To validate the reliability and replicability of the measurements, intraobserver variability was evaluated using different statistical tests, and showed excellent results with a high degree of repeatability for D_{max} and D_{med} measurements. The consistency of the D_{min}, however, was much lower, and therefore the authors decided to reject it for this analysis.

Based on data on transference energy described previously with endolaser or radiofrequency,[3,4,16] the mean D_{max} (9.6 mm) will require a LEED of 60 J/cm, and therefore group 1 is close to the reported threshold of efficacy.[3] In contrast, group 2 (the high-energy dose protocol) seems to be sufficiently treated, attaining a LEED range of 109 to 116 J/cm in all segments. The authors tried to study this in relation to the diameter changes. Group 2 showed a greater reduction of D_{med} than group 1 (standard treatment) throughout the entire study. This reduction reached statistically significant differences when analyzed throughout the study period using the linear model of repeated measures, because of more evident differences on day 4 and month 1. D_{max} reduction was also higher for group 2, but only became statistically significant on day 4, probably because of the small sample size. At 6 months, overall reductions were observed in D_{max} (54.4% vs. 44.6%; P = not significant) and D_{med} (83% vs. 62.5%; $P < 0.0074$). The occlusion rate was 100% at 6 months, which is a very good result and similar to what was reported in the first clinical experience with ClosureFAST.[6] Therefore, the authors were unable to show differences in the occlusion rate along the 6-month study period. During a mean follow-up of 151 days with the overall study population, none of the 67 limbs showed groin neovascularization, in concordance with results reported by other authors.[17,18]

This study has some limitations: it is not randomized nor blinded, and includes a small number of patients, potentially limiting the statistical power of the results. It would have been nice to show RFA be more effective in larger veins, but although D_{max} shrinkage was higher for group 2, it reached statistical significance just at the fourth day, probably because of the sample size. This study is ongoing. The clinical significance of these anatomic findings is not clear because of the high closure rate during the study period.

CONCLUSIONS

The results derived from this study support the theory that a high-energy variation of the standard method of RFA promotes greater ablation and produces more shrinkage more quickly, at least for medium vein diameters (preoperative, 6.75 mm). In other words, the evolutive process can be accelerated through fibrosis in medium-sized veins, and could potentially reduce the probability of recanalization and the procedure's efficacy in terms of clinical setting. With the supplied levels of energy, none of the patients in this study experienced skin burns or indicated symptoms related to saphenous nerve neuritis. Using an accurate tumescent anesthesia technique is a critical step in avoiding these complications. Further studies are needed to evaluate the implications in terms of mid-term and long-term clinical efficacy.

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