Impact of Great Saphenous Vein Foam Sclerotherapy on Quality of Life and Photoplethysmography Findings in Chronic Venous Insufficiency: One-Year Follow-up

FELIPE COELHO NETO, MD, MSc, PhD,*† RODRIGO GOMES DE OLIVEIRA, MD, MSc,* FERNANDO THOMAZINHO, MD, MSc,‡§ ANNA PAULA WEINHARDT BATISTA, PhD,‖ AND IRUENA MORAES KESSLER, MSc, PhD†

BACKGROUND Ultrasound-guided foam sclerotherapy (UGFS) for treatment of chronic venous insufficiency (CVI) has been attracting significant interest over the past 20 years. It is a minimally invasive technique that comprises a safe treatment option and has yielded good results, especially in cases of advanced disease, with high rates of wound healing.

OBJECTIVE To examine clinical, ultrasound, and photoplethysmography outcomes after a 1-year follow-up of UGFS for CVI.

MATERIALS AND METHODS Twenty-nine legs classified as C4, C5, or C6 of the CEAP classification were included. Patients answered the VEINES questionnaire on quality of life and symptoms. and their venous filling time (VFT) was measured using photoplethysmography before and 45, 180, and 360 days after treatment of CVI with UGFS.

RESULTS The results showed statistically significant improvements in VEINES quality-of-life and symptom scores and in VFT measured by photoplethysmography and a reduction in great saphenous vein diameter ($p < .0001$) at 45, 180, and 360 days after treatment with UGFS.

CONCLUSION Ultrasound-guided foam sclerotherapy demonstrated efficacy and resulted in high satisfaction levels, confirmed by improvement in questionnaire scores, venous refilling time, and ultrasound findings.

The authors have indicated no significant interest with commercial supporters.

Ultrasound-guided foam sclerotherapy (UGFS) for treatment of chronic venous insufficiency (CVI) has been attracting significant interest over the past 20 years.[1] It is a minimally invasive technique that comprises a safe treatment option and has yielded good results, especially in cases of advanced disease, with high rates of wound healing.[2]

Short-term meta-analyses and randomized studies of minimally invasive techniques have demonstrated effectiveness, high rates of technical success, and good clinical results.[3–5] However, despite the good technical and clinical results published in the literature,[6] medium- and long-term follow-up studies have shown elevated recanalization rates among patients treated with UGFS.[7]

Regarding the impact on quality of life, a randomized trial comparing the outcomes of foam, laser, and surgical treatments in patients with CVI demonstrated that, over a mean follow-up period of 6 months, disease-specific quality of life was slightly worse after treatment with foam than after surgery.[7] Figueiredo and colleagues[8] followed patients treated with UGFS for 5 years and found that more than 50% of the sample showed partial or total recanalization with reflux, but this outcome did not have an impact on

*Pontifícia Universidade Católica do Paraná (PUCPR), Londrina, PR, Brazil; †Universidade de Brasília (UnB), Brasília, DF, Brazil; ‡Hospital Vascular de Londrina, Londrina, Brazil; §USC—Universidade do Sagrado Coração, Bauru, Brazil; ‖Hospital Israelita Albert Einstein, São Paulo, Brazil

ISSN: 1076-0512 • Dermatol Surg 2019;00:1–9 • DOI: 10.1097/DSS.0000000000002063

quality-of-life assessment results, when compared with those of patients who did not have recanalization or reflux.

Objective analysis of variables that can have an impact on the quality of life of patients treated with sclerotherapy would be of great practical value, but such an analysis has yet to be performed. Objective criteria such as venous filling time (VFT) obtained by photoplethysmography (PPG), residual great saphenous vein (GSV) caliber, and postsclerotherapy ultrasound recanalization profile may exhibit correlations with the subjective data obtained from disease-specific quality-of-life questionnaires.

This study was therefore designed to examine clinical, ultrasound, and PPG outcomes after a 1-year follow-up of GSV UGFS for treatment of patients with CVI by means of a quality-of-life and symptom questionnaire developed specifically for venous disease and an analysis of venous occlusion rate, VFT measured by digital PPG, and saphenous vein diameter, both conducted before and at 45, 180, and 360 days after treatment.

Materials and Methods

This open, prospective study was conducted at the vascular surgery ambulatory of a public hospital in Brasília, DF, Brazil, from December 2012 to August 2014. Eligible participants were all patients aged 18 years and older who had lower-limb CVI with GSV reflux and clinical staging classified as C4, C5, or C6 according to the clinical manifestations, etiologic factors, anatomic distribution of disease, and pathophysiologic findings (CEAP) classification[9] from foam sclerotherapy ambulatory. Patients with acute or nonrecanalized deep vein thrombosis on ultrasound and patients with varicose veins unrelated to GSV reflux were excluded with the purpose of obtaining a uniform sample. Patients with thrombophilia, active cancer or cancer in follow-up, lung disease, or peripheral arterial insufficiency with ankle-brachial index <0.9 were also excluded.

The study was approved by the Ethics Committee at the Hospital Regional da Asa Norte, Brasília, Brazil (approval number 06791512.1.0000.5553). Written informed consent was obtained from all participants before their inclusion in the study. This study was conducted in accordance with the provisions of the Helsinki declaration and the Clinical Research Best Practices.

Duplex Ultrasound Examination

All examinations were standardized and performed by the same physician (F.C.N.). Patients were examined using a MyLab 40 (Esaote, Genoa, Italy) ultrasound unit with a 10- to 12-MHz multifrequency transducer, while standing with their weight on the contralateral limb, with the limb being examined in external rotation, and with the calf musculature relaxed, maintaining stability. The deep vein system was examined for acute or historic venous thrombosis; the superficial vein system was examined with particular attention to the saphenofemoral and saphenopopliteal junctions and the great and small saphenous veins. Reflux in the saphenous vein was induced by manual compression of the calf and defined as reverse flow with duration exceeding 0.5 seconds.[10] The outer diameters of the saphenous vein were measured on the transverse view including the vein wall at 3 points: (1) at 3 cm from the saphenofemoral junction, (2) at the midthigh level, and (3) at the knee-joint line. The mean of the 3 measurements was used for statistical analysis. Control ultrasound examinations of treated saphenous veins were also performed at 45, 180, and 360 days after completion of treatment, and the ultrasound reflux profile was classified as follows: occluded, patent with reflux, or patent without reflux.

Digital Photoplethysmography

A Hadeco (Hayashi Denki CO. LTD, Kawasaki, Japan) PPG unit was used to measure postexercise VFT in a seated position, with the limb hanging, as described by Sam and colleagues.[11] All measurements were taken at the same time of day in the same examination room. The PPG probe was attached to the skin using adhesive tape, varying the position on each patient to avoid areas with trophic lesions caused by CVI, from 13 to 39 cm above the medial malleolus and 1 to 2 cm posterior of the subcutaneous margin of the tibia. All areas with scarring, protruding varicose

veins, perforating veins, pigmentation, or lipodermatosclerosis were avoided. The sites used for PPG probe placement were recorded to enable later measurements to be taken at the same place on each patient. With the patient immobile, the unit was set to perform automatic signal calibration, and as long as a stable baseline signal was obtained, exercises were initiated. The patient performed 10 dorsiflexion and plantar flexion movements within 15 seconds and was then requested to remain at rest as immobile as possible. Ejection of blood from the skin and the curve of subsequent refilling were recorded and then the unit printed the venous filling curve. Measurements were performed 3 times at 2- to 5-minute intervals for each limb, and the mean of the 3 measurements was used for analysis. Normal VFT was defined as ≥20 seconds. VFT was measured before and after completion of treatment with UGFS using the same probe placement height, measured from the sole of the foot.

Quality-of-Life and Symptom Questionnaire

The Venous Insufficiency Epidemiological and Economic Study—Quality of Life/Symptom (VEINES-QOL/Sym) questionnaire, validated for use in Brazil,[12] was used to assess the impact of disease on quality of life. The questionnaire was administered to each patient in the form of an interview by the same researcher (F.C.N.) according to the proposed follow-up. Aspects related to symptoms, work and personal activities, and psychological impact of CVI are covered by the VEINES-QOL/Sym questionnaire. The questionnaire is composed of 2 parts, one focused on quality of life (VEINES-QOL subscale) and the other on symptoms related to CVI (VEINES-Sym subscale), providing 2 numerical variables for the purpose of statistical analysis.

Regarding the VEINES-Sym subscale, 5 response options are provided: "every day," "several times a week," "once a week," "less than once a week," and "never." For the purpose of statistical analysis, the responses "every day," "several times a week," and "once a week" were grouped as "no improvement," while "less than once a week" and "never" were grouped as "improvement."

Sclerotherapy Technique

Patients were positioned in the lateral decubitus position ipsilateral to the GSV to be treated in an attempt to facilitate the exposure of the path of the vein. Punctures were guided by ultrasound in the affected GSV and in the varicose tributaries, using a Scalp (also known as Butterfly needle) 21, 23, and 25 gauge and/or Jelco 20, depending on the depth of the vein. It was decided to always perform at least 1 puncture in the affected GSV and a minimum of 1 puncture in the varicose tributaries, regardless of the depth of the vein. In cases that a single puncture for GSV was performed, the preferred site was at distal thigh. If 2 punctures were performed, the preferred options were one at the middle thigh and other at the distal thigh. If there was the need for completing the treatment, the session was conducted with 1 or more punctures, as required in each case. Foam was produced by the mixture of 1 or 3% polidocanol with ambient air in a 1:4 ratio, depending on the caliber of the vein to be treated, according to medical assistant's judgment. The procedure was performed using a three-way tap, connected to disposable 3-mL syringes with polidocanol and air, respectively. The maximum total volume of foam injected in 1 session was 10 mL, which was performed under echographic view. The procedures followed the European Guidelines recommendations.[13]

Patients were advised to remain at rest for 2 to 5 minutes after injection, avoiding body movement and Valsalva maneuver, if there were no complaints. In situations in which a large volume of foam was echographically identified in the deep system, the patient was asked to perform maneuvers of plantar dorsiflexion to mobilize the foam.

After the treatment with foam sclerotherapy, compression was achieved using 15 to 23 mm Hg or 20 to 30 mm Hg compression stockings, which were worn day and night for 7 days and taken off only for personal hygiene. From the seventh day onward, it was recommended to wear stockings only during the day. No bandages were applied. When the target veins were not occluded completely, additional sessions were conducted until complete occlusion was achieved.

Additional sessions were conducted through 1 or more punctures, as needed in each case, at 7-day intervals.

Statistical Analysis

All data were analyzed using IBM SPSS Statistics, version 23.0 (SPSS, Inc., IBM Company, Chicago, IL), and the level of significance was set at $p < .05$. The Wilcoxon test was used to determine increases in VFT and VEINES-QOL subscale scores. The McNemar test was used to compare VEINES-Sym subscale scores.

Results

A total of 32 patients were included sequentially in the study, and 91 percent (29/32) completed 180 days and 360 days of follow-up. Mean patient age was 52 years (range: 36–76 years), and 86% were women. The left lower limb was involved more frequently, in 62% of cases (18/29). Table 1 shows treatment characteristics and the principal signs and symptoms before treatment are listed in Table 2.

Active or healed ulcers were observed in 66% of patients, 24% of patients had arterial hypertension, and 13% had Type 2 diabetes. Regarding CEAP classifications, 10 (35%) patients were classified as C4, 7 (24%) were classified as C5, and 12 (41%) were classified as C6. All patients had primary as etiological classification, superficial as anatomical classification, and reflux as pathophysiologic classification. Eighteen (63%) patients were treated in a single session, 10 (34%) required 2 sessions, and just 1 patient (3%) required a third session to complete treatment.

The mean volume of foam used per session was 8.4 mL.

The mean number of punctures used for treatment was 4.1 punctures per patient (range: 3–7). A single puncture for GSV treatment was the option in 48% (14/29) of the sample. Two punctures were performed in 34% (10/29), and the choice was 3 or more punctures in 17% (5/29) patients.

At 45 days after treatment, all symptoms had improved, with statistical significance, with the exception of paresthesia and throbbing, as shown in Figure 1.

The mean VFT, calculated using digital PPG immediately before the intervention and 45, 180, and 360 days after completion of treatment, revealed statistically significant improvements, as illustrated in Figure 2.

At the same consultations as the VFT measurements were taken, the VEINES-QOL and VEINES-Sym subscales were administered before treatment and 45, 180, and 360 days after completion of treatment. The data collected after treatment showed statistically significant improvements in means when compared with the baseline data. Figure 3 illustrates the data from the quality-of-life subscale, and Figure 4 illustrates the data from the symptom subscale.

Patency of the treated GSV and residual diameters was assessed before treatment and at 45, 180, and 360 days

TABLE 1. Epidemiological Data and Treatment Characteristics of Patients With Varicose Veins and Incompetent Great Saphenous Veins

Characteristics of Treatment	*Statistical Data*
CEAP classification—C4	35% (10)
CEAP classification—C5	24% (7)
CEAP classification—C6	41% (12)
Family history of DVT	14% (4/29)
No. of punctures	4.1 (3–7)
No. of sessions	1.4 (1–3)
Mean volume of sclerosant per session (mL)	8.4 (4–10)

CEAP, clinical manifestations, etiologic factors, anatomic distribution of disease, and pathophysiologic findings; DVT, deep venous thrombosis.

TABLE 2. Signs and Symptoms Present Before Treatment

Symptoms	*Percentage (%)*
Pain	79% (23/29)
Heaviness	79% (23/29)
Tiredness	83% (24/29)
Burning sensation	83% (24/29)
Paresthesia	59% (17/29)
Itching	90% (26/29)
Edema	65% (19/29)

after completion of treatment to observe the veins' behavior after UGFS. Early control ultrasound examinations at 45 days after treatment showed that 90% of the treated veins had been occluded (24/29). At 6-month follow-up, an elevated recanalization rate was observed, with only 43% of veins still occluded, reducing to 37% at 1 year after treatment. Figure 5 illustrates the occlusion rate over the follow-up period. For statistical analysis, the post-treatment ultrasound status was clustered in 2 groups: occluded GSV or patent GSV.

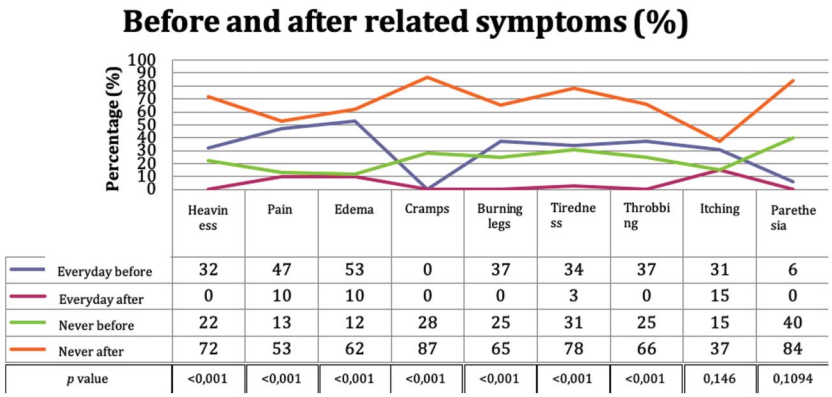
With relation to residual diameters, there was a considerable reduction in measurements over the 1-year follow-up period. The mean GSV diameter before treatment was 8.4 mm. Six months later, mean diameter had reduced by 47%, to 4.5 mm. Mean diameter at the 12-month follow-up was 3.8 mm, with a 55% accumulated reduction from the pretreatment baseline. The reductions in GSV calibers over the follow-up period were statistically significant, as shown in Figure 6.

Twelve patients of the sample were classified as C6. Of these, 7 (58%) had their ulcers healed after 45 days of treatment, 9 (73%) had their ulcers healed after 180 days of treatment, and at the end of the follow-up of the 360-day study, 83% of the C6 patients had healed ulcers. There was no ulcer recurrence in the C5 group. Reintervention with EGUS was performed in 16 patients (55%) throughout the follow-up of the study.

Discussion

This study assessed the impact of treatment of severe CVI with UGFS. Significant improvements were observed in quality-of-life and symptom scores and in VFT as measured by digital PPG, and there were considerable reductions in the diameters of the treated GSV. Despite the favorable clinical impact, there was around 63% recanalization of treated saphenous veins, in line with other published data.[14]

Minimally invasive techniques for treatment of lower-limb varicose veins, such as intravenous thermoablation and UGFS, have become the first choice for axial treatment of the GSV.[15] These techniques offer reduced



	Heaviness	Pain	Edema	Cramps	Burning legs	Tiredness	Throbbing	Itching	Paresthesia
Everyday before	32	47	53	0	37	34	37	31	6
Everyday after	0	10	10	0	0	3	0	15	0
Never before	22	13	12	28	25	31	25	15	40
Never after	72	53	62	87	65	78	66	37	84
p value	<0,001	<0,001	<0,001	<0,001	<0,001	<0,001	<0,001	0,146	0,1094

Figure 1. Symptoms relief after treatment.

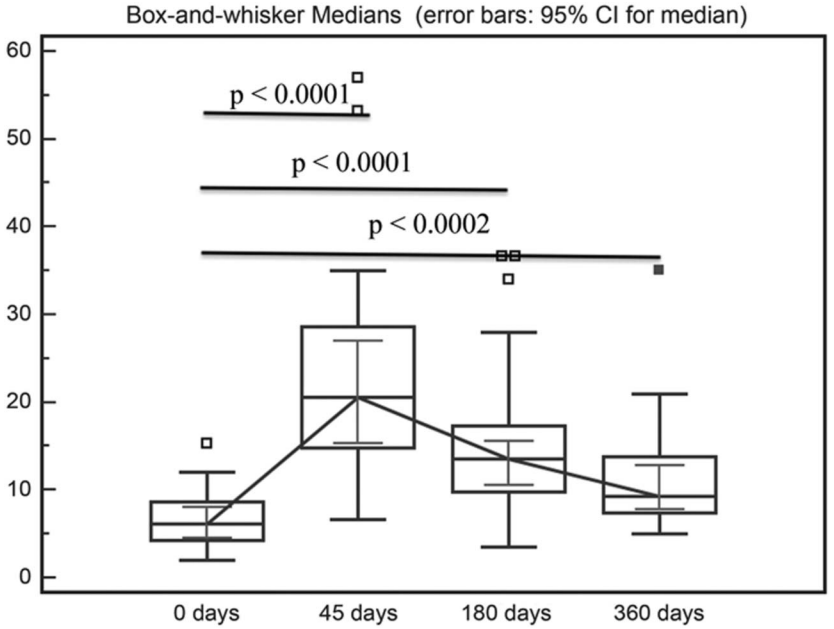


Figure 2. Improvement in venous filling time measured by photoplethysmography after treatment. CI, confidence interval.

morbidity, can be conducted in the office, and enable patients to return to daily activities and to work more quickly.[2–4,15] Treatment of CVI with UGFS is of particular interest, especially for the most severe presentations of this disease, with rates of ulcer healing of around 85%.[2,15,16]

Regarding provoking definitive venous occlusion, it is well established in the literature that foam sclerotherapy has venous reflux relapse rates seen on ultrasound that exceed those of other methods and recanalization rates can reach 64% in 5 years.[17] However, despite these high recanalization rates, UGFS nevertheless achieves persistent clinical improvements, and the patients treated with this method gain relief from their symptoms. Venermo and colleagues[14] conducted a study comparing surgery,

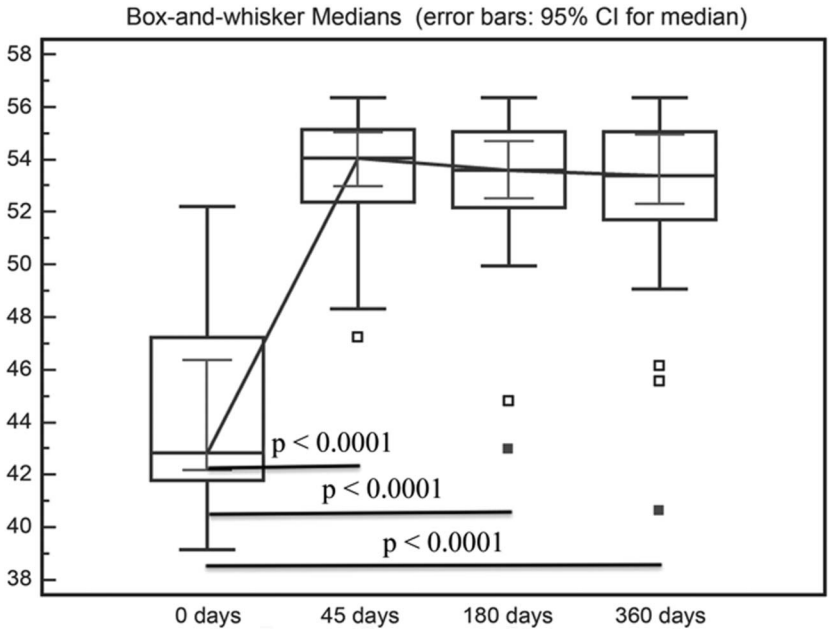


Figure 3. Improvement in VEINES-QOL scores after treatment. CI, confidence interval.

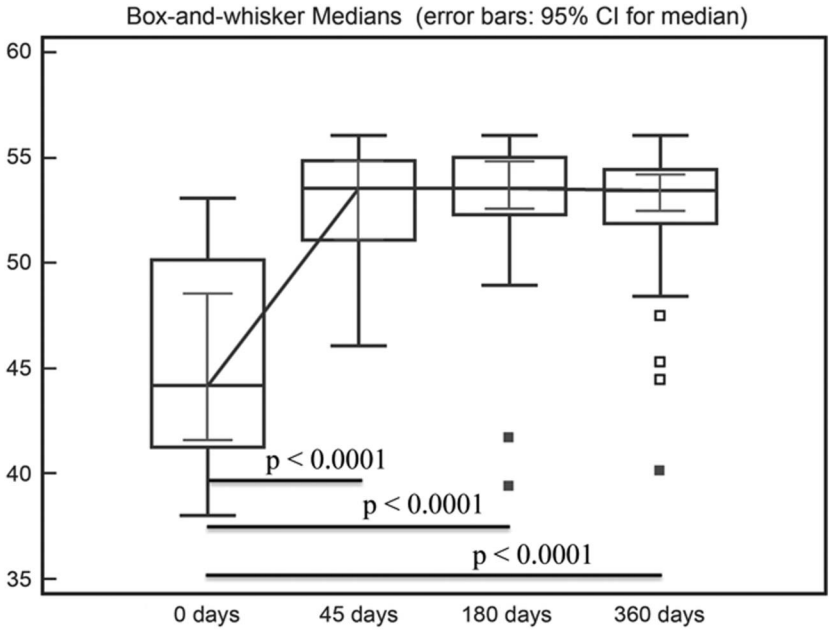


Figure 4. Improvement in VEINES-Sym scores after treatment. CI, confidence interval.

intravenous laser, and UGFS, in which they stated that despite a total recanalization rate of 49% in the group of patients treated with UGFS, the improvements in quality-of-life scores were similar over a 12-month follow-up period. They also pointed out that in a subset of patients treated with UGFS whose GSV diameters exceeded 9 mm, the occlusion rate at 1 year was less than 40%, contrasting with 75% among patients with saphenous diameters smaller than 6 mm.[17]

In another study,[18] there was a 70% reduction in venous diameter after UGFS over 12-month follow-up, which is similar to the results observed in this study. The drastic reduction in the diameters of GSV treated using UGFS may be one of the features that contribute to maintenance of improved quality of life among these patients. However, a 12-month follow-up period may be too short to enable evaluation of the impact of recanalization on these patients.

Ultrasound-guided foam sclerotherapy offers excellent clinical results over the short term.[4,19] The authors' healing rate were more than 80%, and the authors demonstrated that UGFS is effective to avoid recurrence, in accordance with previous study.[20]

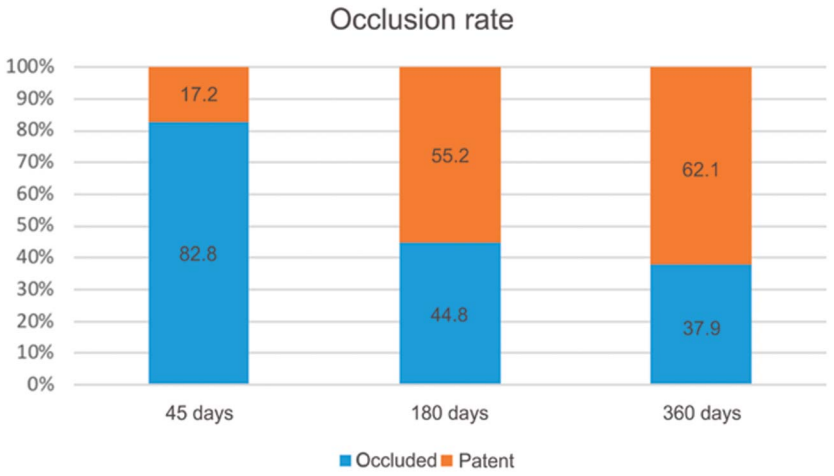


Figure 5. Venous occlusion rate over time.

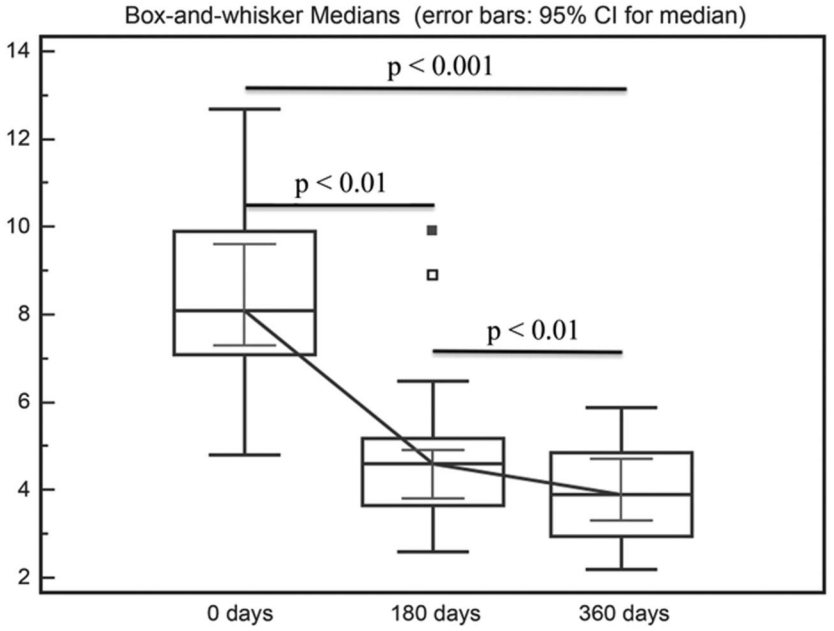


Figure 6. Reduction in venous diameter after treatment. CI, confidence interval.

Lloret and colleagues[20] demonstrated higher rates on healing ulcers when isolated GSV reflux is present. The presence of deep venous system reflux or perforator vein incompetence decreases the healing rates. This study demonstrates that the positive impacts on quality of life and on VFT are maintained over a 12-month follow-up period, despite identification of a high rate of recanalization of the treated GSV and a progressive deterioration of VFT after treatment. The progressive deterioration in VFT may be explained by the recanalization of superficial veins over time, not related to GSV recanalization. Studies with longer follow-up would make it possible to assess the impact of post-UGFS recanalization on quality-of-life scores, on the rate of varicose vein relapse, and on the need for additional interventions.

Acknowledgments The authors thank Beatriz Balducci Coelho and Lenisa Vilas Boas for their valuable contribution.

References

1. Cabrera J, Cabrera García-Olmedo J. Nuevo método de esclerosis en las varices tronculares. Patología Vasc 1995;4:35–7.
2. Neto FC, de Araujo GR, Kessler IM, de Amorim RF, et al. Treatment of severe chronic venous insufficiency with ultrasound-guided foam sclerotherapy: a two-year series in a single center in Brazil. Phlebology 2015;30:113–8.
3. Biemans AA, Kockaert M, Akkersdijk GP, van den Bos RR, et al. Comparing endovenous laser ablation, foam sclerotherapy, and conventional surgery for great saphenous varicose veins. J Vasc Surg 2013;58:727–34 e1.
4. Rasmussen LH, Lawaetz M, Bjoern L, Vennits B, et al. Randomized clinical trial comparing endovenous laser ablation, radiofrequency ablation, foam sclerotherapy and surgical stripping for great saphenous varicose veins. Br J Surg 2011;98:1079–87.
5. Lattimer CR, Azzam M, Kalodiki E, Shawish E, et al. Cost and effectiveness of laser with phlebectomies compared with foam sclerotherapy in superficial venous insufficiency: early results of a randomised controlled trial. Eur J Vasc Endovasc Surg 2012;43:594–600.
6. Rathbun S, Norris A, Stoner J. Efficacy and safety of endovenous foam sclerotherapy: meta-analysis for treatment of venous disorders. Phlebology 2012;27:105–17.
7. Brittenden J, Cotton SC, Elders A, Ramsay CR, et al. A randomized trial comparing treatments for varicose veins. N Engl J Med 2014;371:1218–27.
8. Figueiredo M, de Araujo SP, Figueiredo MF. Late follow-up of saphenofemoral junction ligation combined with ultrasound-guided foam sclerotherapy in patients with venous ulcers. Ann Vasc Surg 2012;26:977–81.
9. Eklöf B, Rutherford RB, Bergan JJ, Carpentier PH, et al. Revision of the CEAP classification for chronic venous disorders: consensus statement. J Vasc Surg 2004;40:1248–52.
10. Labropoulos N, Tiongson J, Pryor L, Tassiopoulos AK, et al. Definition of venous reflux in lower-extremity veins. J Vasc Surg 2003;38:793–8.
11. Sam RC, Darvall KA, Adam DJ, Silverman SH, et al. Digital venous photoplethysmography in the seated position is a reproducible noninvasive measure of lower limb venous function in patients with isolated superficial venous reflux. J Vasc Surg 2006;43:335–41.
12. De Moura R, Gonçalves G, Navarro T, Britto RR, et al. Transcultural adaptation of VEINES/QOL-Sym questionnaire: evaluation of quality of life and symptoms in chronic venous disease. J Vasc Bras 2011;10:17–25.

13. Pannier F, Rabe E; for the Guideline Group. Results from RCTs in sclerotherapy: european Guidelines for sclerotherapy in chronic venous disorders. Phlebology 2014;29(1 Suppl):39–44.

14. Venermo M, Saarinen J, Eskelinen E, Vähääho S, et al. Randomized clinical trial comparing surgery, endovenous laser ablation and ultrasound-guided foam sclerotherapy for the treatment of great saphenous varicose veins. Br J Surg 2016;103:1438–44.

15. Silva M, Burihan M, Barros O, Nasser F, et al. Results of treatment of severe chronic venous insufficiency with ultrasound-guided polidocanol foam. J Vasc Bras 2012;11:206–11.

16. Pang KH, Bate GR, Darvall KA, Adam DJ, et al. Healing and recurrence rates following ultrasound-guided foam sclerotherapy of superficial venous reflux in patients with chronic venous ulceration. Eur J Vasc Endovasc Surg 2010;40:790–5.

17. Chapman-Smith P, Browne A. Prospective five-year study of ultrasound-guided foam sclerotherapy in the treatment of great saphenous vein reflux. Phlebology 2009;24:183–8.

18. Chen CH, Chiu CS, Yang CH. Ultrasound-guided foam sclerotherapy for treating incompetent great saphenous veins—results of 5 years of analysis and morphologic evolvement study. Dermatol Surg 2012;38: 851–7.

19. Coelho Neto F, de Araujo G, Kessler I. Evaluation of quality of life and photoplethysmography in patients with chronic venous insufficiency treated with foam sclerotherapy. J Vasc Bras 2015;14:145–52.

20. Lloret P, Redondo P, Cabrera J, Sierra A. Treatment of venous leg ulcers with ultrasound-guided foam sclerotherapy: healing, long-term recurrence and quality of life evaluation. Wound Repair Regen 2015; 23:369–78.

Address correspondence and reprint requests to: Felipe Coelho Neto, Av. Maringá, 2655, CEP: 86010-010, Londrina, PR, Brazil, or
e-mail: contato@drfelipecoelho.com.br