Original Article

Phlebology

Phlebology
2016, Vol. 31(1) 34–41

DOI: 10.1177/0268355514557854
phl.sagepub.com

Chronic venous leg ulcers: Effects of foam sclerotherapy on healing and recurrence

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Abstract

Introduction: Ultrasound-guided foam sclerotherapy is a minimally invasive treatment option used for ablation of axial and perforator reflux for chronic venous ulceration. Active ulceration presents a significant health burden in both the primary and secondary care setting. The objective of this study is to determine ulcer healing rates at 24 weeks and 12 months, and ulcer recurrence rates at one year for chronic venous ulcers after ultrasound-guided foam sclerotherapy.
Methods: Between 2007 and 2012, 54 patients underwent ultrasound-guided foam sclerotherapy for clinical, aetiological, anatomical and pathological C6 ulcers. All patients were followed up clinically, and venous duplex was performed on all legs before and after treatment. A prospectively maintained database was analysed to determine venous truncal occlusion rates, 24-week and 12-month healing and recurrence rates (using Kaplan–Meier survival analysis).
Results: Fifty-seven ulcerated legs, 39 primary and 18 with recurrent superficial venous reflux were analysed. Median time of active ulceration at presentation was 15.2 months (range 5 months to 17 years). At a median follow-up of 2.7 months, 90% (51 legs) achieved full truncal occlusion after one session, 4% (2) short segment occlusion and 5% (3) failed to occlude and one patient died and was lost to follow-up; 13/57 (23%) required a second session of treatment for completion of treatment, recanalisations and to treat perforator disease, 88% (50/57) ulcers healed at a median of 5.3 months (interquartile range 2.9–8.4 months) following their first ultrasound-guided foam sclerotherapy treatment. The 24-week and 12-month estimated healing rates were 53% and 72%, respectively. The estimated 12-month recurrence rate was 9.2%. There were no reported incidences of deep venous thrombosis or neurological symptoms.
Conclusion: This study affirms the role of ultrasound-guided foam sclerotherapy as a safe and effective option for abolition of superficial reflux.

Keywords

Foam sclerotherapy, venous ulceration, chronic venous insufficiency, leg ulcers, venous reflux

Introduction

Chronic venous ulceration (CVU) has an adverse impact on health-related quality of life (HQRL), causing morbidity and distress[1] and places a considerable socioeconomic burden on the National Health Service.[2,3] CVU will affect up to 1% of Europeans in their lifetime, and the point prevalence of open venous ulceration is estimated at up to 0.3%.[4,5] The condition can affect any age group, but is particularly common, and problematic, in the elderly population, contributing to morbidity.

The ESCHAR trial in 2003 showed surgical correction of superficial venous reflux (SVR), when compared to compression alone, led to a significant reduction in ulcer recurrence rates at one year (12% in the surgery plus compression group vs. 28% in the compression only group),[6] although healing rates were shown to be similar in both groups. Long-term results of this study reported by Gohel et al.[7] confirmed a sustained reduction in ulcer recurrence in the surgery group.

Since the time of the ESCHAR trial there has been a move away from varicose vein surgery,[8] with the development and results of more minimally invasive techniques including endothermal ablation and ultrasound-guided foam sclerotherapy (UGFS).

NICE have recognised the magnitude of this chronic condition. Based upon recommendations from the

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Venous Forum of the Royal Society of Medicine, NICE have recently issued guidelines recommending immediate referral to a vascular service for bleeding varicose veins and prompt referral, for intervention, for symptomatic varicose veins, which include active venous ulcers clinical, aetiological, anatomical and pathological (CEAP) C6, which have not healed within two weeks and healed CEAP C5 healed venous ulcers.[9] The guidelines recommend radiofrequency ablation and endovenous laser treatment as first-line treatment for confirmed symptomatic varicose veins and truncal reflux, and foam sclerotherapy if these treatments are unsuitable. Several randomised trials and systematic reviews compared the efficacy and cost-effectiveness of these treatments.[10–14] Minimally invasive treatments have been included in varicose vein commissioning guidelines, to improve patient safety by 'reducing risks of people developing venous ulceration and improving healing and recurrence rates in people already affected by ulceration'.[15]

Studies of UGFS on healed and open venous ulcers, CEAP C5 and C6 have shown promising results.[16,17] Venous ulceration as demonstrated in a population study, is particularly troublesome for patients since it may take over nine months to heal with 66% lasting more than five years and is a premise for active intervention as to improve quality of life and reduce burden the healthcare system.[18]

In this paper, we report results on a large series of patients with long-standing open venous ulcers (CEAP 6) who were treated with foam sclerotherapy. We demonstrate the efficacy of this treatment in a population with poor compliance with compression bandaging alone. The objective of this study is to determine ulcer healing rates at 24 weeks and 12 months, and ulcer recurrence rates at 1 year for chronic refractory venous ulcers.

Methods

Patients and setting

Data were extracted and analysed from a prospectively maintained computerised database for patients undergoing UGFS. The target population were patients presenting to the vascular unit with open venous ulcers (CEAP 6) of more than four weeks duration between March 2007 and October 2012. SVR and the level of venous incompetence were confirmed on venous duplex scan. The patients were assessed by a vascular nurse specialist for suitability for UGFS based on the venous duplex scan. Patients with purely SVR defined as truncal incompetency of the great saphenous vein (GSV), short saphenous vein (SSV), anterior accessory saphenous vein (AASV) were offered foam sclerotherapy and put in compression bandaging. This was managed by the vascular service whilst awaiting their treatment. SVR with segmental deep venous insufficiency (DVI) and SVR with perforator disease were also offered foam sclerotherapy. Duration of ulcer, comorbidities, previous varicose vein surgery, warfarinisation, previous deep venous thromboses (DVTs) were all recorded on initial assessment, and these data were extracted from patients' notes for analyses. Twelve patients had had previous varicose vein surgery and presented with saphenofemoral junctional incompetency and three had UGFS previously; all of these patients were offered foam sclerotherapy. Compliance and adequacy of compression bandaging in the community was assessed by a vascular nurse practitioner on initial consultation. Tolerance of bandaging, duration of compression and grades of compression were assessed.

Patients with concurrent arterial disease and ulcers that were found to have alternative aetiology (basal cell carcinoma (BCC), squamous cell carcinoma (SCC) and vasculitis) were excluded from the final analysis. Whilst waiting for UGFS, patients were treated with graduated compression over non-adherent dressing. Thirteen patients had healed prior to treatment; they were still treated for CEAP C5 disease, but were excluded from this study.

Ultrasound-guided foam sclerotherapy

UGFS was performed in an outpatient setting. The refluxing saphenous trunk and varicosities were identified on duplex. The patients were placed in a reverse Trendelenburg position for cannulation with 20 G Leadercath for truncal veins and butterfly for varicosities. Seldinger technique was used to cannulate, and sclerosant foam was injected under direct ultrasound guidance. The foam was prepared by mixing air or physiological gas (carbon dioxide and oxygen) and 3% or 1% sodium tetradecyl sulphate (STS) (Fibrovein®; STD Pharmaceuticals Ltd, Hereford, UK), in a ratio of 3:1. GSV treatment was primarily a combination of 3% and 1% STS with a greater ratio volume of 3% as compared to SSV alone. AASV was treated with 1% (see Table 2). Gas and STS were oscillated manually between two 5 ml syringes connected by a 5 μm filter, a minimum of 20 times. With the patient then in the Trendelenburg position, foam was injected in 3 ml aliquots with intervals and plantar and dorsiflexion exercises between injections, under ultrasound supervision.

An anterograde approach was used to target the GSV, AASV, SSV and/or refluxing varicosity. A bidirectional technique was used in some patients with STS foam injected into a second Leadercath placed in a

retrograde direction in the GSV, usually to the lower thigh, to treat the distal portion of the vessel. This method places concentrated 1% foam directly within the lumen of the distal GSV, as opposed to direct injection of calf varicosities, which can promote subsequent thrombophlebitis.

Post treatment, patients were asked to plantar and dorsiflex their ankle to clear any foam from the deep system. All patients were placed into a multilayer compression bandaging, or a thigh length Class II compression stocking with appropriate non-adherent ulcer dressings.

Outcome measures and assessment of the ulcerated limb

On retrospective analysis, all patients had an initial review at median 2.7 months. Leg ulcers were examined by a constant senior vascular nurse specialist, and duplex venous ultrasound was performed on all patients to assess the extent of occlusion and recanalisation; this was defined as anterograde or retrograde flow in a previously occluded segment. The ulcer was examined by the same vascular nurse specialist, and patients were discharged on complete healing. Complete healing was defined as complete re-epithelisation of the skin. Any complications were recorded in a prospectively maintained database and incorporated into the results.

Outcome measures were 24-week and 12-month healing rate and 12-month recurrence rates. Patients who had been discharged prior to 12 months were called up for a phone consultation to determine whether an ulcer had recurred since healing. Local ethical approval was obtained from the research and audit committee.

Statistical analysis

Ulcer healing and recurrence following UGFS was estimated using Kaplan–Meier survival analysis. Time to healing was calculated from first foam treatment to outpatient appointment when healing was noted. Recurrence was calculated from the date of healing to active ulceration within a year. Patients who died or were lost to follow-up were censored. Analysis was conducted using IBM SPSS Statistics v22 for Windows.

Results

A total of 57 legs in 54 patients with chronic active ulceration (CEAP C6) were treated with UGFS between 12 February 2007 and 2 October 2012. Seven patients were excluded from the analysis (three mixed aetiology arterial component, two BCC, one SCC on biopsy and one systemic lupus erythematosus), 13 healed their ulcers at the time of treatment, leaving 54 patients and 57 legs for analysis.

Patient demographics, comorbidities, previous DVTs, warfarinisation and duration of ulcer are shown in Table 1.

Median (interquartile range, IQR) volume of foam used was 9 ml (6–9.5 ml). Thirty-nine (68%) legs were primary and 18 (32%) recurrent varicose veins; of these 16 patients had previous varicose vein surgery and two had had foam sclerotherapy treatments. Refluxing segments of GSV, SSV and AASV are shown in Table 2.

Occlusion of truncal veins

Of the 57 legs treated for ulceration, at median 2.7 months at first follow-up, 51/57 (90%) achieved complete occlusion after one treatment session. One patient died and was lost to follow-up, 2/57 (4%) had partial short segment occlusion and 3/57 (5%) had failed treatments. These 5/57 (9%) patients needed a second session for completion of treatment; 13/57 (23%) required a second session of treatment due to three failed treatments, four recanalisations, two short segment occlusions and four treatments to incompetent perforator disease (Table 3). Patients were rescanned to investigate

Table 1. Patient demographics and characteristics, $n = 54$ patients.

Demographics		
Male	28	
Female	29	
Age (years, median)	68	
$n = 57$ ulcers	CEAP C6	Total (%)
Ulcer		
Primary	39	68
Recurrent	18	32
Duration symptoms (median, range)	14.5 (5 months–17 years)	
No. of circumferential ulcers	2	
Relevant comorbidities		
Osteoarthritis	11	
Obesity	10	
Type II DM	8	
COPD	3	
Immobility	3	
Orthopaedic lower limb surgery	3	
Family history	2	
Warfarin	4	
DVT	2	

COPD: chronic obstructive pulmonary disease; DVT: deep venous thrombosis.

Table 2. Treatment characteristics.

	Refluxing segment		
	GSV	SSV	AASV
Ulcer			
Primary	34	5	0
Recurrent	12	4	2
Foam used (median volume ml)			
1%	7.8	3	15
3%	9.3	6.1	0
Approach			
Anterograde	37	9	2
Bidirectional	9	0	0
Technique			
Seldinger	29	7	0
Butterfly	4	0	2
Seldinger/butterfly	13	2	0

GSV: great saphenous vein; SSV: short saphenous vein; AASV: anterior accessory saphenous vein.

Table 3. Treatment characteristics.

	No. of legs
Repeat foam	13
Recanalisation	4
Short segment occlusion	2
Perforators	4
Failed treatment	3
Complications	
Thrombophlebitis	2
Transient chest tightness	1
Pain/discomfort	2

ongoing or slow healing ulceration and to treat and contributing SVR.

Great saphenous vein. Complete occlusion was seen in 44/46 (96%) legs for GSV reflux after one session: one patient had partial segment occlusion and one treatment failed, full occlusion was achieved with a second treatment. One patient died before first follow-up. A total of eight patients required a subsequent treatment; one partial occlusion, one truncal incompetence, three recanalisation of GSV and three for small perforating veins. Complete occlusion was achieved after a minimum of two treatments.

Short saphenous vein. Complete occlusion was seen in 7/9 (78%) legs for SSV reflux after first treatment. One treatment failed, one had partial occlusion, one required a further session for varicosities. 100% occlusion rate was seen after a second session.

Anterior accessory saphenous vein. Complete occlusion was seen in both patients treated for refluxing anterior accessory saphenous vein.

Ulcer healing

Complete healing was observed in 50/57 (88%) at a median (IQR) follow-up of 5.3 months (2.9–9.3) following their first UGFS treatment (Figure 1). The median ulcer duration prior to treatment was 14.5 months (range 5 months to 17 years). Almost all patients had been in some form of compression bandaging in the community. Median follow-up from time of treatment was 23.1 months (IQR 15.7–30.5). Of the 57 ulcers active at treatment, complete healing was seen in 28/57 at 24 weeks and 38/57 had healed by 12 months. Using Kaplan–Meier survival analysis, 53% ulcers healed at 24 weeks and 71.8% at one year; 12/57 (21%) patients took over a year to heal.

The 12 patients who took over a year to heal were a particularly challenging group with complex backgrounds. The mean age was 70 years. Ten were primary and two recurrent (previous varicose vein surgery). The median time ulcer present prior to treatment 17.5 months (range 6 months–17 years). Five of these were chronically infected ulcers (clinically and on wound swabs) and the size of the ulcers ranged from 10 cm^2 to 200 cm^2. Two patients had a history DVTs and deep venous incompetence, three were on warfarin and eight had risk factors for poor healing such as osteoarthritis and obesity. Three had lymphoedema and chronic venous hypertension. One patient had a concurrent BCC on a separate ulcer. Five of these 12 patients required repeat foam treatment: one failed treatment, one partial short segment occlusion and three due to incompetent perforators. Five had recurrent ulcers after complete healing at 4.6, 14, 22.8, 24.9 and 25.1 months.

Three patients are still under follow-up with chronic longstanding healing ulcers, two of these have required repeat treatments, and all ulcers are improving. Five died within a year of treatment due to other comorbidities and were lost to follow-up.

Ulcer recurrence

Ulcer recurrence was analysed on 50 legs with a median follow-up of 15.2 months (IQR 9.1–24.7). Recurrence was seen in 4/50 (8%) at 12 months; the four patients recurred at 4.6, 5.5, 8.3, 9.5 months. At 24 months, a further six patients were identified with recurrent ulceration as part of their follow-up for chronic venous disease; as long-term two-year follow–up, data were not

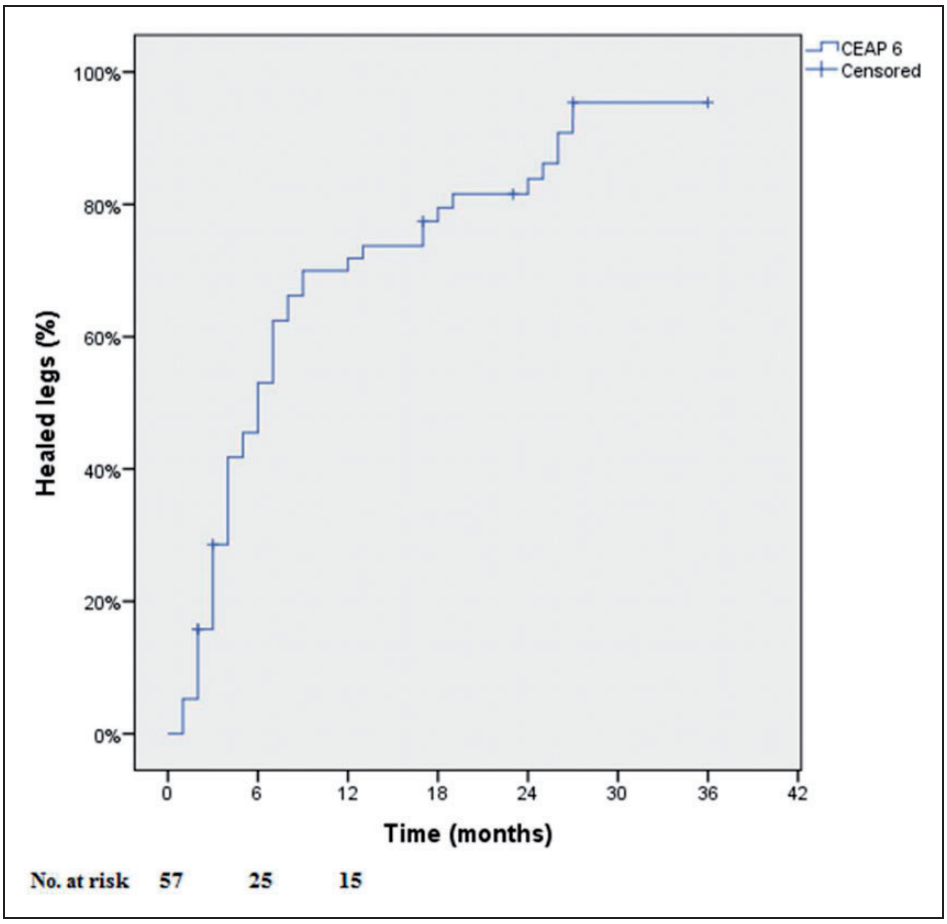

Figure 1. Kalpan–Meier analysis of ulcer healing in 57 limbs treated with UGFS for C6 disease. CEAP: clinical, aetiological, anatomic and pathophysiological.

available, these recurrences have not been included in the analysis. Using Kaplan–Meier survival analysis, the one year estimated recurrence rate was 9.2 (Figure 2). Median ulcer-free periods for all legs treated was 13.7 months (IQR 6.2–18.2).

Of the four recurrences within 12 months, one patient subsequently healed in four-layer compression bandaging and was discharged. Two patients were treated for recurrent reflux and required a second foam treatment due to recanalisation and incompetent perforators; they are currently being managed in four layer compression bandaging and healing but under follow-up. One patient re-ulcerated and was discharged with compression bandaging and community follow-up.

Late recurrences were seen at 14, 18.2, 22.8, 24.9, 25.1 and 25.4 months and three of these six patients required a second treatment.

Complications

Twenty-two patients were lost to follow-up: five died of unrelated causes, 15 were discharged as their ulcer healed prior to a year and were unreachable and two moved away. These patients were censored. At time of treatment, one patient complained of transient chest tightness, two complained of pain and discomfort which shortly resolved and there were no reported neurological symptoms. At follow-up, there were no recorded cases of DVT on duplex scan.

Discussion

This study adds to the body of evidence supporting the efficacy of foam sclerotherapy and affirms its place in the treatment of CVU. It specifically reports active long-term venous ulceration in a subset of patients with multiple comorbidities and poor compliance with compression bandaging alone. This sub group represents a significant proportion of those suffering with long-term venous ulcerations. These patients are generally referred late and underrepresented in studies reporting outcomes in varicose vein treatment.

The healing and recurrence rates in our study are comparable to other recently published studies for

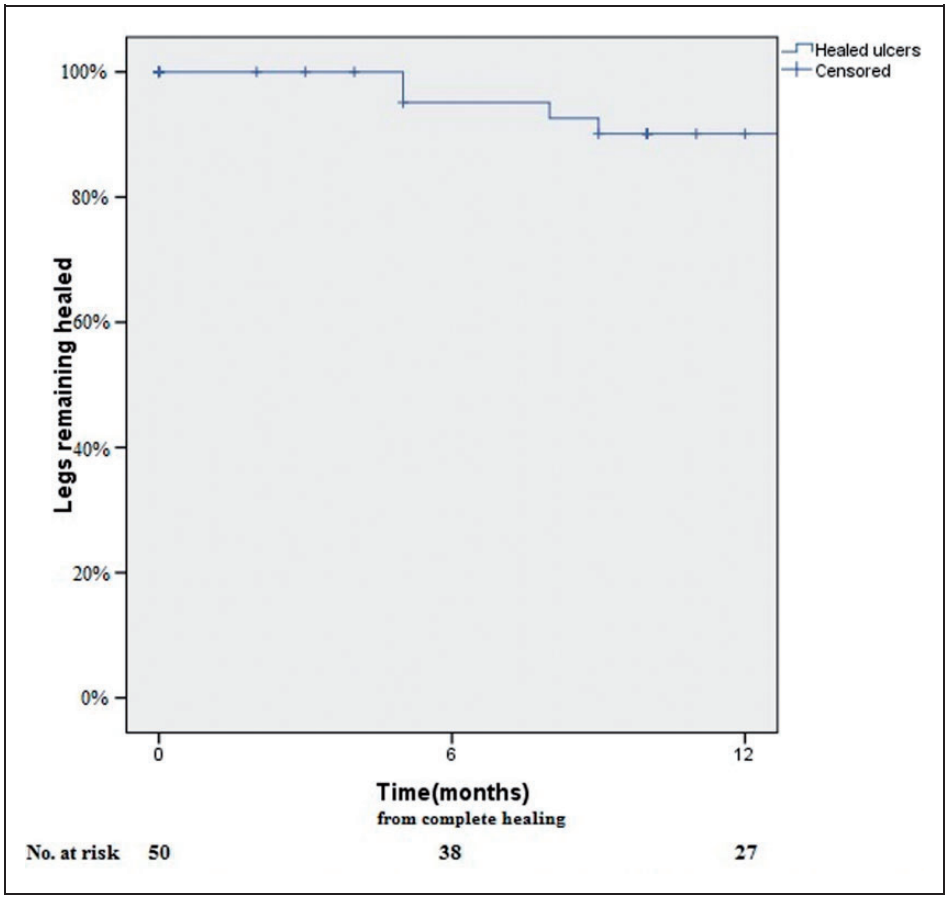

Figure 2. Kalpan–Meier analysis of ulcer recurrence for 50 CEAP 6 ulcer treated that healed after UGFS.

foam sclerotherapy.[15] Healing was observed in 50/57 patients at a median of 5.3 months, many of whom had been in compression bandaging and had ulcers for a median of 14.5 months and ranging up to 17 years.

While in our study healing rates were 53% at 24 weeks and 71.8% at 12 months, Kulkarni et al.[16] reported healing rates 71.1% at 24 weeks and 91.2% at one year. The number of active ulcers they looked at was 37 compared to 57 in this study.

Pang et al.[17] reported a greater powered and well-designed study analysing 82 CEAP C6 ulcers with a healing rate of 82% at a median 1 month. In all, 81% of ulcers healed by six months following treatment compared to our healing rate of 88% at median 5.3 months and 53% ulcers healed at six months. In our study, the median ulcer duration was 14.5 months which was greater by comparison to Pang et al. which had a median ulcer duration of eight months. In legs treated for C6 disease, we reported a median ulcer-free period of 13.7 months (IQR 6.2–18.2), Pang et al. reported 22 (IQR 9–32) months.

Our early occlusion rates, 90% at median 2.7 months after the first session of UGFS, were in keeping with the results of Kulkarni et al. (92.5%); however, a drawback of both these studies is that patients were not all routinely scanned at one year and inevitably there were recanalisation. We reported four recanalisations at 8.3, 9.4, 21.3 and 25.1 months. Thirteen patients required a second treatment: four recanalisations, two short segment occlusion, four perforators and three for failed treatments. All patients were rescanned at first follow-up and patients with non-healing or recurrent ulcers had further duplex scans, and thus recanalisations were identified. Incompetent perforators were treated for patients with non-healing ulceration on the basis that they were feeding the ulcer bed and were treated with a second foam treatment.

Studies reporting outcomes of foam sclerotherapy have all reported repeat sessions as a part of the treatment pathway for abolishing SVR. Lattimer et al.[13] reported a randomised clinical trial comparing early outcomes of three weeks and three months of endovenous laser ablation (EVLA) with concurrent phlebectomies (currently the first-line recommended treatment option) with UGFS. UGFS significantly outperformed EVLA in cost, treatment duration, pain, analgesia requirements and recovery. Although additional sessions of foam were required, UGFS was reported as

3.15 times less expensive. Interim reports of the same trial demonstrated EVLA and UGFS were equally effective at abolishing global venous reflux with overall success of 41% and 43%, respectively.[14] The high reflux rate was not related to deterioration in quality of life, assessed by venous clinical severity score, quality of life Aberdeen varicose vein questionnaire and the saphenous treatment score, thus indicating that this reflux was largely asymptomatic.

The ESCHAR trial remains the only randomised study that compares conservative management with surgical intervention on ulcer healing rates and recurrence.[6] Its evidence has been the cornerstone of the argument that, although recurrence is reduced, healing rates are similar with intervention and with and compression therapy alone. The intervention of choice, however, has now moved away from surgery to minimally invasive options. Yet these treatments have not been compared to compression therapy alone in a randomised setting. O'Hare and Earnshaw[19] attempted a randomised trial comparing the healing rates of foam sclerotherapy with compression therapy and failed to recruit enough participants to demonstrate a significant difference. The Early Venous Reflux Abolition (EVRA) trial,[20] Imperial College, London, is randomising patients with active ulceration into early or delayed endovenous treatment and will assess time of ulcer healing as a primary endpoint. It is expected to conclude in 2017 and its results may be pivotal in demonstrating improved healing rates with aggressive early intervention. Alden et al.[21] published a retrospective study looking at 95 active ulcers and assessed healing rates and one-year recurrence of those managed with compression bandaging and those offered minimally invasive treatments of UGFS, radiofrequency ablation and both. In all, 31% of the group had UGFS. The review showed ulcer-healing rates and recurrences were significantly improved with intervention when combined with compression, than with compression alone. However, the results of this study may be challenged as this was a retrospective review of clinical records and the 'compression arm' had a higher incidence of DVI. In our practice, all patients undergo compression therapy following their treatment.

It is widely accepted that aggressive intervention is indicated for the treatment of symptomatic varicose veins. Minimally invasive treatment has now superseded surgery in terms of outcomes, feasibility and cost effectiveness. NICE currently recommends foam sclerotherapy as a treatment option after endovenous laser and thermal ablation.[9] Foam sclerotherapy has shown promising results on ulcer healing and recurrence by treating superficial reflux as the primary treatment of choice and also as an adjunct to other therapies. It has also been shown to be the least expensive. In addition, it has been used to treat the 'terminal source of reflux' through injecting feeding vessels at the base of the ulcer bed and successfully achieved ulcer healing[22]; this can be explored to treat resistant ulcers that may not be amenable to treatment with endovenous ablation.

Our results support existing data and establish the role of foam sclerotherapy in the treatment of CVU. We provide clear evidence that foam sclerotherapy in experienced hands can be used with minimal risk in this subgroup of patients. Our practice continues to aggressively treat CVU without waiting for the ulcer to heal.

There is, however, a subset of ulcers that are truly recalcitrant and have not healed despite these measures. Alden et al.[21] reported 12.5% of ongoing ulceration despite abolition of truncal reflux; our results report three patients (5.3%) who had ongoing ulceration at time of analysis. The question remains, whether accelerated ulcer healing would occur in a randomised setting of compression bandaging alone to foam sclerotherapy or endovenous catheter-based treatment. A previous attempt at this failed to recruit enough numbers,[18] and with the availability of minimally invasive techniques with minimal risks to a frail and elderly population, conducting such a trial may not be appropriate to this subset of patients. Comparing foam sclerotherapy to endovenous treatment could be possible, but again, in this subset of patients, many would have been unsuitable for a catheter-based treatment (which relies on a relatively direct course of the long saphenous vein for catheterisation). As well as abolishing truncal reflux, foam also offers the option of treating the local 'feeding' vessels at the ulcer bed itself and still remains the most cost-effective option.

We acknowledge that there are limitations to this study which result from a retrospective analysis of patients presenting to our unit with CVU. We report our results but have not compared with any other group. A randomised controlled trial would be of benefit in providing further evidence as expected from the EVRA trial.[20] Optimal conservative management of the ulcers in the community was not clearly defined in the context of this study and was assessed by a vascular nurse specialist.

We treated patients with a mixture of disease patterns: SVR alone, SVR and segmental DVI and SVR and perforator disease. The ESCHAR trial[6] has demonstrated reduced ulcer recurrence in those with SVR and concurrent segmental deep venous disease.

For the purpose of ulcer recurrence, the prospective database of patients was not designed to follow-up patients up to one year after the ulcer had healed. Patients who were discharged from clinic prior to one year were contacted by phone at least twice before being declared lost to follow-up.

Based on our experience of UGFS, and on published data, we continue to aggressively treat and manage patients with active venous ulceration as soon as possible after appearance of the ulcer. A clear pathway for referral to our unit is used in conjunction with the NICE guidelines for prompt referral through the primary care setting. This subset of patients is managed with a multi-disciplinary approach, with prompt treatment and regular follow-up with a specialist vascular nurse practitioner.

Conflict of interest

None declared.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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