Issa *et al. Egypt J Radiol Nucl Med (2024) 55:113*
https://doi.org/10.1186/s43055-024-01280-5

Egyptian Journal of Radiology and Nuclear Medicine

RESEARCH

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Ultrasound-guided foam sclerotherapy versus four-layer compression only for treatment of chronic venous ulcers

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Abstract

Background Chronic venous ulcers are prevalent, its incidence (1%) in the general population. Venous ulcers are quite a challenge for physicians to treat. Among the numerous pathological causes, venous hypertension remains the leading cause. This study aims to compare the safety, efficacy, short-term complications, factors affecting wound healing as well as pathological outcomes of ultrasound-guided foam sclerotherapy (UGFS) in conjunction with the four-layer compression bandage in the management of chronic venous ulcers.

Methods Retrospective analysis of a hundred patients with chronic venous ulcers treated between December 2018 and December 2021. Two groups were studied: the control group, which received conventional compression, and the study group, which underwent injection sclerotherapy and conventional compression. Punch skin biopsies were taken from both groups before and after treatment to compare the histological effects of the two methods.

Results Complete healing was achieved in 100% of the patients, with a shorter healing time in the study group (34.82 ± 4.7). Additionally, the degree of inflammation was significantly decreased but there was a higher local complication rate in the study group.

Conclusions UGFS in conjunction with the compression bandage showed superior clinical and pathological results but, risk of complication was increased.

Keywords Venous ulcer, Varicose veins, Sclerotherapy, Inflammation

Background

Chronic venous ulcers are a common problem, Prevalence of chronic venous ulcers is estimated about 1% in USA. It is also considered highly costly, costing 3 billion dollars annually [1]. The most common complications are pain, bleeding, infection, disfigurement, and, most importantly, a high recurrence rate [1].

Chronic venous ulcers are primarily caused by chronic venous insufficiency [2]. In patients with venous ulcers, primary varicose veins with GSV reflux are the most common clinical presentation [3]. It is estimated that 6% of patients with varicose veins will develop venous ulcers during their lifetime [4].

Lower extremity varicose veins treatment options include great saphenous vein stripping and minimally invasive techniques [5]. In addition to the relatively high association with recurrence, some surgical options necessitate more advanced anesthetic options and a more

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extended hospital stay. Unlike open surgery, sclerosant injection under ultrasound guidance does not require hospitalization or advanced anesthesia and has a lower recurrence rate [6, 7]. Under ultrasound guidance, foam sclerotherapy is performed, thereby achieving local drug targeting and reducing the complications of sclerotic agent leaks [8, 9].

Sclerotherapy patients report less painful procedures and a quicker return to normal activities than surgical patients [10, 11]. However, sclerotherapy has a lower success rate in preventing reflux. Consequently, foam sclerotherapy is favored less by health cost analytics than other invasive methods [12].

In 2007, the Effect of Surgery and Compression on Healing and Recurrence (ESCHAR) trial indicated that the combination of compression and venous stripping for venous reflux did not seem to improve the cure rates. However, compared to compression alone, it significantly reduced recurrence rates of chronic venous ulcers [13, 14].

Minimally invasive techniques such as endovascular laser ablation, radiofrequency ablation, and ultrasound-guided foam sclerotherapy have progressively come to substitute superficial venous stripping surgery as the superiorly preferred management of choice for early varicose veins (C2/3 disease) because of the outcomes for individuals with advanced C4/6 stays of low significance [15].

Injections of sclerosing agents have been used to treat chronic venous insufficiency for over a century (42), and the accuracy and efficacy of ultrasound-guided injection sclerotherapy have demonstrated promising results [16].

In this study, we aimed to achieve the best results by treating incompetent perforators with ultrasound-guided sclerotherapy and venous hypertension with a four-layer compression bandage.

Methods

In this study, we retrospectively analyzed the clinical and pathological outcomes of 100 patients who presented to the vascular outpatient clinic at Minia University Hospital between December 2018 and December 2021. After having the institutional board approval (No. 667/2/2023), patients were then divided into two groups: the control group, which received four-layer compression alone, and the study group, which received incompetent perforator US-guided micro-foam injection in conjunction with compression.

The inclusion and exclusion criteria of this study were as follows:

Inclusion criteria:

- Patients > 18 Years old.
- Patients with chronic venous insufficiency.
- Patients having active venous ulcers = CEAP (clinical-etiological-anatomical-pathophysiological) six classifications at the time of intervention. [17].
- Patients with comorbidities intervening with any surgical operation.
- Diabetic patients with poor wound healing.

Exclusion criteria:

- Patients < 18 years old.
- Peripheral arterial obstructive disease.
- Venous thromboembolism.
- Patients with patent foramen ovale.
- Pregnancy.
- Allergy to polidocanol.
- Infection of the lower limbs.
- Deep vein obstruction (by Duplex scan).
- Patients who were unable to walk or were confined to bed.
- Patients with unfavorable clinical conditions.

Clinical outcome is defined as complete healing of the treated ulcer, and pathological results are defined as reduction in the cellular inflammatory infiltrates and degree of inflammation in the punch skin biopsy [18, 19].

All patients underwent clinical history taking, local examination, and Duplex scan. The patients old CT venographies were revised, to evaluate the presence of venous hypertension (presence of focal stenosis or occlusion in the proximal venous tree).

Additionally, the patients were subjected to the venous clinical severity scores (VCSS), which is used to assess those with venous disease that that is complementary to the CEAP classification. The score includes 10 clinical parameters (pain, varicose veins, venous edema, skin hyperpigmentation, inflammation, induration, number of ulcers, durations of ulcers, size of ulcers, and compliance with compression therapy). Each item is graded from zero to three depending on severity (None = 0, Mild = 1, Moderate = 2, Severe = 3) [20]. Parameters were measured in both groups. Moreover, patients underwent measurement of the ulcer diameter, punch biopsy of the ulcer, and, before and after treatment, colored photography.

Patients were subjected to the treatment based on their personal preference following comprehensive clinical examination and within the constraints of inclusion and exclusion criteria.

UGFS technique

By superficial probe (9L-D) (logic E9 ultrasound machine, USA), each incompetent perforator is scanned

in horizontal and longitudinal views, and the perforator is punctured with a 23-gauge butterfly needle. One cc of 3% polidocanol *(Aethoxysklerol@; Kreussler* Pharma, Wiesbaden, Germany) is agitated with 4 cc room air until the foam is formed. The foam is immediately injected into the vein and manually directed under ultrasound guidance into the perforator. When the perforator is filled with foam, pressure is maintained over the perforator's connection to the deep venous system for two minutes. A maximum of 10 ml of foam is utilized per session (Fig. 1). The leg is then compressed with ice bandages or an ulcer wrap with multiple layers (Unna boot dressing), (Medicopaste, Graham-Field, Hauppage, New York).

The dressing composed of four layers, the first is a soothing agent, zinc oxide with iron oxide, it is applied with the second layer is a wrapping gauze, forming a semirigid paste bandage, and the third layer is a compressive bandage and the fourth is a creep bandage [21].

Statistical analysis

Statistical methods described and summarized the demographic and clinical information gathered retrospectively. When applicable, the Chi-square test was applied to categorical variables. All statistical tests were

Table 1 Base line data of and the associated comorbidities between the two groups; this is represented in the form of age, sex, the size of the treated ulcers in cm and the number of perforators

Variable	Compression, injection *N* = 50	Compression only *N* = 50	Significance
Age			
Mean ± SD	57.8 ± 6.4	57.62 ± 6.6	*P* = 0.89
Sex N (%)			
Male	25 (50%)	24 (48%)	*P* = 0.84
Female	25 (50%)	26 (52%)	
Ulcer size	3.37 ± 0.52	3.37 ± 0.62	*P* = 0.94
Number of perforators			
1	14 (28%)	13 (26%)	*P* = 0.82
2	19 (38%)	17 (34%)	
3	17 (34%)	20 (40%)	
DM	28 (56%)	30 (60%)	*P* = 0.69
Venous HTN	27 (54%)	26 (52%)	*P* = 0.84
Systemic HTN	26(52%)	25(50%)	*P* = 0.84
Previous trauma	20(40%)	19(38%)	*P* = 0.84
Obesity	22(44%)	22(44%)	*P* = –

The venous hypertension in the associated comorbidities was assessed by reviewing the patients previous CT venography to confirm the presence of stenosis, occlusions or collaterals

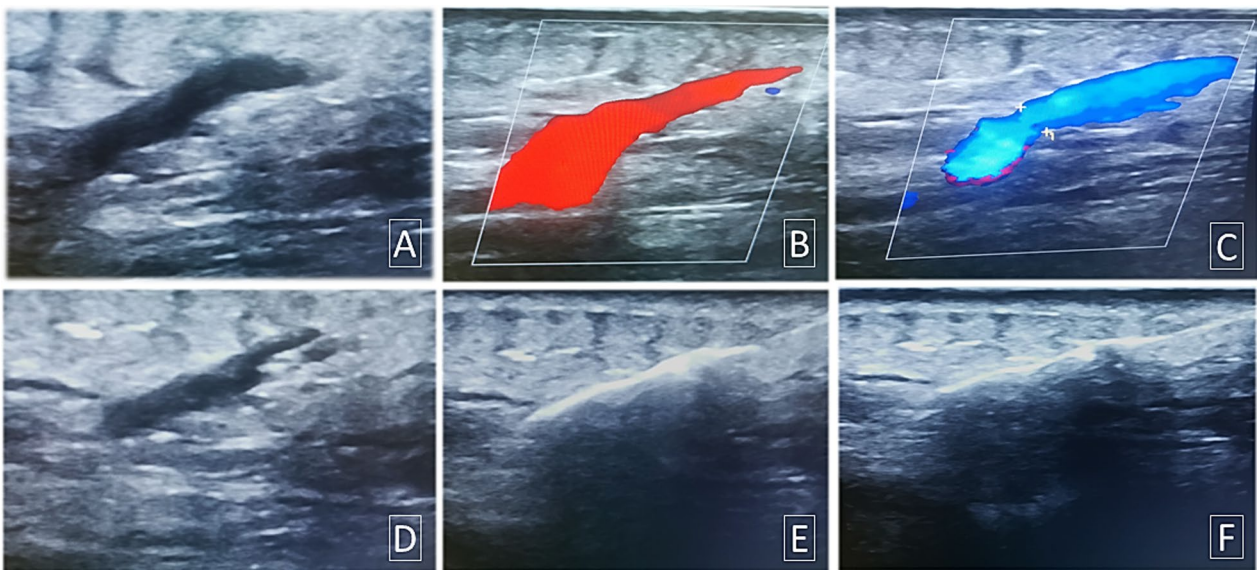


Fig. 1 USGF technique; **A** US examination showing perforator crossing the facial line. **B** Color Doppler examination showing direction of blood flow. **C** reversal of flow upon proximal augmentation detecting its incompetence. **D** advancement of the needle into the perforator. **E** During foam injection into the perforator. **F** at the end of the procedure, notable collapse of the incompetent perforator

Table 2 Compression duration and duration of healing among two studied groups

Variable	Compression + injection *N* = 50	Compression only *N* = 50	Significance
Total compression bandage duration(days) (Means ± SD)	50.52 ± 5.6	55 ± 5.4	*P* = 0.001*
Duration to complete healing (days) (Means ± SD)	34.82 ± 4.7	55.1 ± 5.3	*P* = 0.001*

*Statistical significance with *P* value < 0.05

Table 3 Pathological findings (degree of inflammation and ulceration) [18] among two studied groups before and after the procedure

Variable	Compression, injection *N* = 50	Compression only *N* = 50	Significance
Degree of inflammation and ulceration before the procedure			
1	0 (0%)	2 (4%)	
2	15 (30%)	17 (34%)	*P* = 0.31
3	35 (70%)	31 (62%)	
Degree of inflammation and ulceration after the procedure			
1	41(82%)	9 (18%)	*P* = 0.001*
2	9 (18%)	35 (70%)	
3	0 (0%)	6 (12%)	

*Statistical significance with *P* value < 0.05

two-sided, and a p-value < 0.05 was regarded as statistically significant. The statistical analyses were performed using SPSS version 25. Cox regression hazards test was used to analyze the factors affecting the wound healing in treated patients (Table 1).

Results

Table 2 represents the time for complete healing of an active ulcer "clinical success," there were a significant reduction in the total compression duration and a significant reduction in the healing time in the study group as compared with the control group.

Table 3 shows that the degree of inflammation and ulceration detected pathologically were significantly reduced in the injection /compression group rather than the control group.

In Table 4, we summarized the complications founded in both groups, and superficial thrombophlebitis, pigmentations and recurrence rates were the statistically significant ones (Table 5).

Table 4 Complications in both studied groups (variables measured according to venous ulcer severity score)

Variable	Compression, injection group *N* = 50	Compression only *N* = 50	Significance
Pain Scale			
Mean ± SD	2.72 ± 0.67	2.66 ± 0.66	*P* = 0.65
DVT	2 (4%)	3 (6%)	*P* = 0.65
Superficial thrombophlebitis	14 (28%)	5 (10%)	*P* = 0.02*
Pigmentations			
Mild	14 (28%)	29 (58%)	*P* = 0.001*
Moderate	22 (44%)	21 (42%)	
Severe	14(28%)	0 (0%)	
Recurrence	2 (4%)	13 (26%)	*P* = 0.002*
Ulcerations	11(22%)	4 (8%)	*P* = 0.05

*Statistical significance with *P* value < 0.05

Table 5 Cox proportional hazards regression for factors affecting healing time in the study sample

Variable	Hazard ratio	95% CI	*P* value
Type of treatment	58.64	(32.47–60.23)	0.001*
Venous HTN	2.35	(1.22–4.52)	0.01*
Systemic HTN	2.09	(1.09–4.01)	0.027*
Age	0.95	(0.91–0.99)	0.02*
Previous trauma	1.21	(0.69–2.09)	0.5
Diabetes	1.43	(0.86–2.38)	0.17
Gender	0.73	(0.43–1.24)	0.24
Obesity	1.12	(0.64–1.94)	0.69

*Statistical significance with *P* value < 0.05

Ulcerations may occur as a result of injection; this usually happens when there is a leaking of the sclerosant material to the superficial layers of the skin; usually, it is limited and usually resolve spontaneously on further follow-up.

Cox proportional hazards regression analysis revealed that the type of treatment, presence of venous hypertension, systemic hypertension and the patients age are the major factors which affects the rate of ulcer healing.

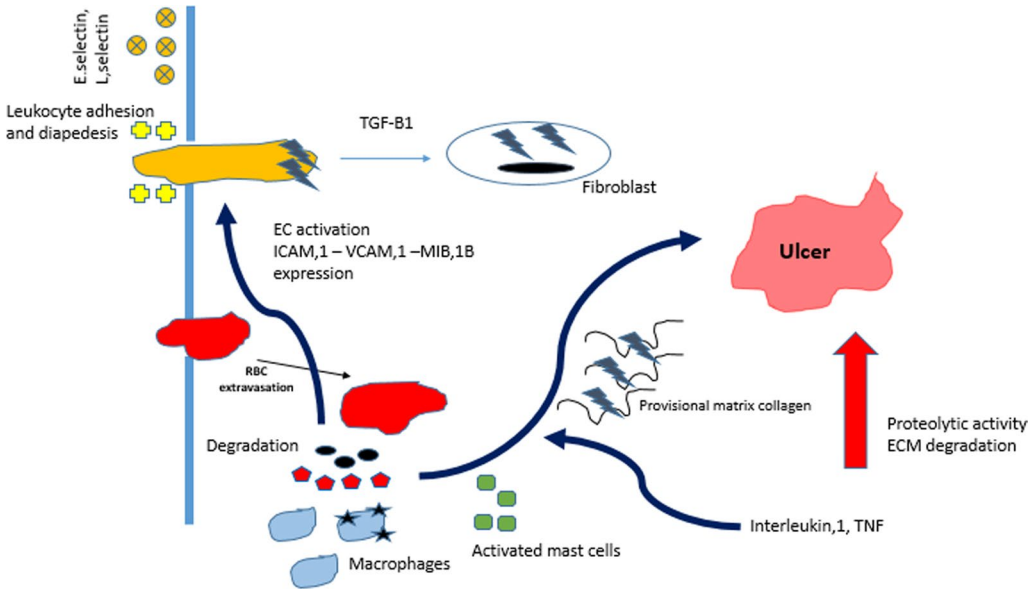


Fig. 2 Pathophysiology of venous ulcer

Discussion

Numerous hypotheses have been proposed to explain the etiology of venous ulcers. The theory of venous reflux and obstruction is one of the most widely accepted explanations for the underlying pathophysiology of venous leg ulcers [22, 23].

The major pathophysiological mechanism in venous ulcers is inflammation within the venous circulation that causes increased hydrostatic pressure, and thus increased ambulatory pressure with inflammatory response [24–26] (Fig. 2).

The hallmark of leg ulcers is based on the treatment of the underlying chronic venous disease. Compression therapy does not correct the venous reflux alone, despite its association with healing 65% of the ulcers within almost 24 weeks. Unfortunately, approximately 70% of the patients experience recurrence with cessation of the treatment [27–29], whereas foam sclerotherapy can induce the closure of more than 80% of the treated varicose veins [30, 30].

Few studies found a higher prevalence rate of venous ulcers in women [31], but this has been decreased with age [32, 33], and actually, a more recent study indicated that male patients had a higher risk of developing venous leg ulcers [33]. No gender preference was statistically significant in our study. Being a retrospective study, this does not represent the prevalence in our locality. More prospective, consecutive studies may be required to establish a correlation between gender and prevalence.

The most prevalent treatment for venous ulcers has consisted of leg elevation and multilayered compression therapy for decades [34]. This treatment proved to be an effective method for promoting ulcer healing in up to 70% of treated ulcers. However, if this compression is not maintained, the recurrence rate is depressing, reaching up to 25% in the first year and possibly reaching 100% with a longer follow-up [35].

Ultrasound-guided foam sclerotherapy injection is a widely performed technique due to its low cost, ease of use, good patient tolerability as well as the benefits gained from the associated occlusion of the varicosity network related to the ulcer area, with a reported 54% perforator closure rate and 3% DVT of calf veins [36]. Although cannulation and foam injection of the feeding varicosities appears more straightforward than the percutaneous thermal ablation of the perforator technique, foam sclerotherapy may demonstrate rapid washout in high-flow systems prior to the occurrence of spasm and thrombosis. Additionally, larger veins necessitate larger volumes of the sclerosant agent with higher concentration for successful closure, which may affect the complication rates [37]. Ultrasound-guided foam sclerotherapy has been recommended by the European guidelines for

sclerotherapy in chronic venous disorders in the management of varicose veins in the venous ulcer region [38].

In a prospective study by Pang [39], studying 132 extremities with CEAP C5 or C6 stage, it states that when combined with a compression bandage, cessation of superficial venous reflux utilizing ultrasound-guided foam sclerotherapy injection results in an 81% healing rate in 6 months and 5% recurrence in 2 years. This low recurrence rate seems to be superior to that reached with compression therapy alone (typically 26–28% in 12 months, 40% in 2 years, and 56% in 4 years in the ESCHAR trial) and following superficial venous surgery combined with compression (20% at 2 years and 31% at 4 years in the ESCHAR trial) [13, 14, 40, 41]. In comparison with his results, we had a less complication rate 4% in this study.

Other studies have demonstrated the efficacy and safety of ultrasound-guided foam sclerotherapy in the treatment of varicose veins. For instance, Nesbitt et al. [6] showed that ultrasound-guided foam sclerotherapy and surgery are comparable regarding the recurrence, failure, and vessel recanalization rates. Similarly, Venermo et al. [42], which randomly treated 214 (CEAP class 2 to class 4) venous varicosities with one of three interventions, laser ablation, surgery, or ultrasound-guided foam sclerotherapy, stated that the latter was superior to the remaining treatment modalities in terms of pain relief.

In our study, we reported a 4% recurrence rate in the injection group, which is comparable to or less than that reported by Kulkarni et al. [8], who achieved a recurrence rate of 4.7% of lower limb venous ulcers in a period of 12 months after ultrasound-guided foam sclerotherapy. The recurrence rates in our trial were lower than Grover et al. [43], who managed 54 venous ulcers with foam sclerotherapy and reached a healing rate of 88% at 5.3 months and a recurrence rate of 9.2% at a 1-year duration, this may be due to the combined use of compression bandage in conjunction with the polidocanol micro-foam endovascular injection.

Ultrasound-guided foam sclerotherapy is user-friendly, affordable, minimally invasive, and efficacious. However, it was associated with local skin necrosis as a result of the extravascular sclerosant leakage [44] in addition to DVT and pulmonary embolism [45], possibly due to the spilling of the sclerosant into the deep veins through incompetent perforators.

Regarding the local complications in our study, the commonly encountered complications were superficial thrombophlebitis (28%) in the study group as compared with (10%) in the control group. This result is more than the incidence reported by Thomasset, SC, and Kamhawy et al. [46, 47]. Nonetheless, we achieved the same results in terms of skin pigmentation, with nearly 28% of individuals suffering from severe pigmentation.

To our knowledge, this is the first paper to discuss skin changes pathologically in the context of venous ulceration. In both groups, there was a significant improvement in the inflammatory skin response with a statistically significant reduction in the inflammation and ulceration in favor of the study group, where injections in conjunction with compression were used.

In our multivariate analysis of factors affecting the healing of venous ulcers, the treatment modality employed, the presence of venous hypertension, systemic hypertension, and age were found to be significant. They are comparable to the findings of Labropoulos et al. [48], who hypothesized that factors associated with refractory ulcers include a history of DVT, old age, obesity, and non-adherence to compression therapy.

Although diabetes mellitus may significantly affect the healing process of venous ulcers, DM was not associated with a reduction in the healing rates in our sample. This finding is consistent with other studies [49–51] but contrary to the findings of Margolis et al. We also could not detect any association between hypertension and healing failure [49].

In this study, all selected patients were compliant with compression therapy before and after injection as well as after complete healing. Compression therapy plays a fundamental role in the healing process and increases the recurrence-free period following complete ulcer healing [1].

The limitation of this study was, it was a retrospective one, and a prospective studies will be of added value for gender preference rates. More patient number will enforce our conclusion and more prolonged follow-up needed for the outcome and possible recurrence.

Conclusions

Injection sclerotherapy along with four-layer compression is safe, effective method for treatment of venous ulcers with faster recovery rates, reduced recurrence and improvement of pathological skin inflammatory process.

Figure ligands

Control group

Case1

A 50-year-old male with chronic venous ulcer.

A: Before compression therapy, with notable ulceration and necrosis at the ulcer margin.

B: after 20 days of four-layer compression, with a notable reduction in the ulcer size.

C: At the end of treatment, about 50 days of compression with back to normal skin, complete healing of the ulcer.

Case 2

A 53-year-old male with chronic venous hypertension.

A: Before compression with previous bleeding, solitary stitch was taken at the bed to control the bleeder.

B: After compression with an improvement of the ulcer depth, still notable some skin ulceration.

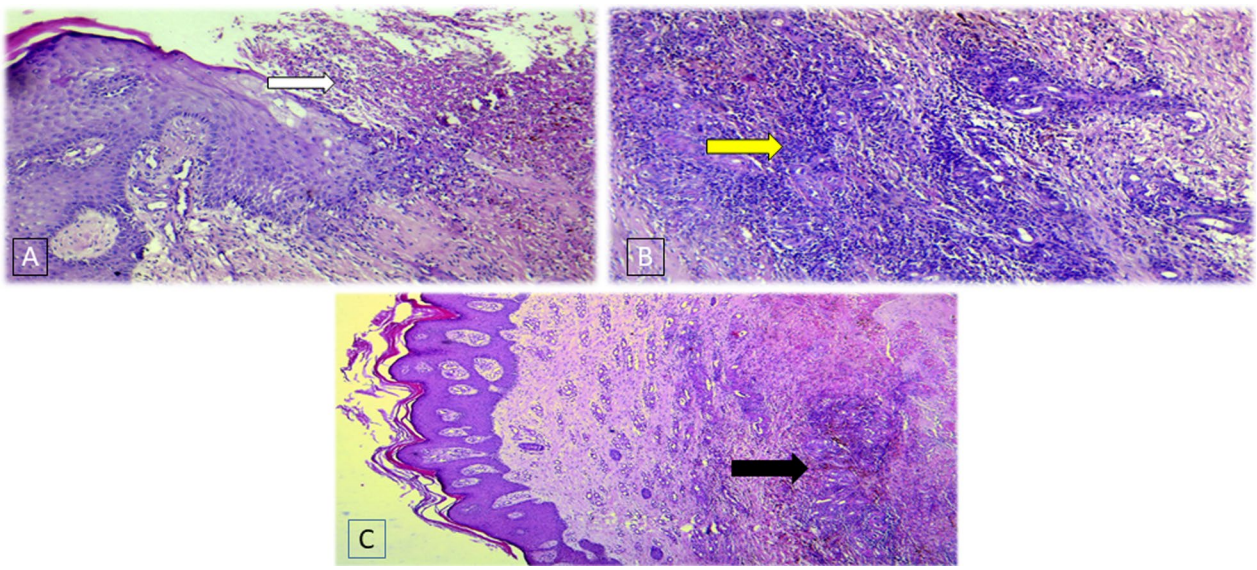
Case 3

A 49-year-old female with marked skin laceration resulting from venous hypertension.

A: Marked skin laceration, superficial ulceration.

B: after compression therapy with reduction in the skin ulceration, scar formation.

Pathological results



A: Punch biopsy in venous ulcer before compression showing marked surface ulceration with necrosis (H&E × 100).

B: Infiltration of the dermis by a severe chronic inflammatory response in venous ulcer before compression (H&E × 100)—Yellow arrow.

C: Punch biopsy in venous ulcer after compression in the previous patient showing improvement of surface ulceration, but the severe chronic inflammatory response is still present in the dermis (H&E × 400)—Black arrow.

Study group (with US foam injection and compression)

Case 1

A 51-year-old female with resistant venous ulcer.

A: Venous ulcer with necrotic margins with associated diffuse cellulitis, surrounding edema, and induration.

B: After compression/injection with marked reduction in the associated cellulitis, clear margins with filling of the ulcer base with granulation tissue.

Case 2

A 65-year-old, obese female with recurrent ulcer not responding to treatment.

A: Active skin ulcer with associated infection.

B: After injection/compression with small superficial ulceration that was monitored with complete healing of the ulcer, small scar tissue is seen on the ulcer bed.

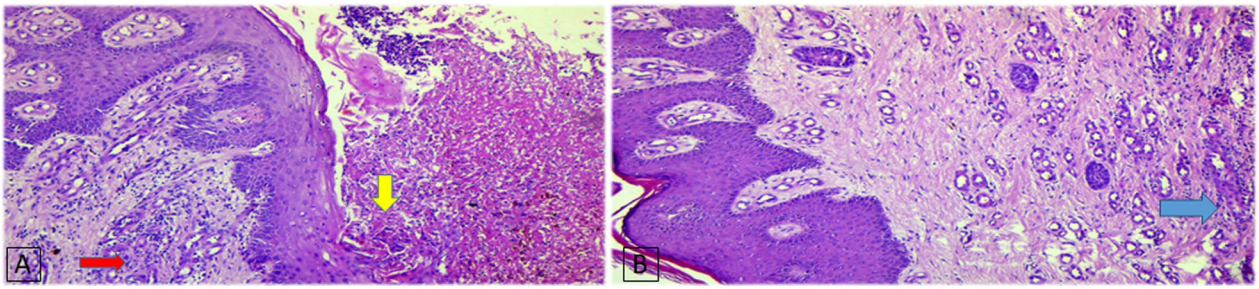
Case 3

60-year-old male with venous leg ulcer over the anterior leg

A: Before treatment, linear ulcer at the anterior leg.

B: After injection/compression, near complete healing of the ulcer with scar formation.

Pathological results



A: Punch biopsy in venous ulcer before compression and injection sclerotherapy showed marked surface ulceration and necrosis (the yellow arrow) with infiltration of the dermis by chronic inflammatory cells (the red arrow) (H&E×100).

B: Punch biopsy in venous ulcer after compression and injection sclerotherapy in the previous patient showing resolution of surface ulceration with the persistence of only mild chronic inflammatory response in the dermis (the blue arrow) (H&E×100).

Abbreviations

CVD	Chronic venous disease
VU, VLU	Venous ulcers, venous leg ulcers
SVR	Superficial venous reflux
ICPV	Incompetent perforator vein
SEPS	Sub-facial endoscopic perforator surgery
USGFS	Ultrasound sonar guided foam sclerotherapy
DVT	Deep venous thrombosis
HTN	Hypertension

Acknowledgements

None.

Author contributions

All authors participated in the study design; material preparation and collection of data were done by "A.I" and "A.Y." The first draft of manuscript was written by "M.N" and "M.S." The statistical results and final manuscript were revised by "R," "A.M" and "T.Z." All authors read and approved the final manuscript.

Funding

None.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval

This study was done in line with declaration of Helsinki. Approval was granted by ethical committee of faculty of medicine. Minia University No. 667:2/2023 "Retrospective registered." Faculty of medicine. Minia University.

Consent to participate

All participants and authors approve the publication of the work; written consent was obtained from all patients or their first-degree relatives.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Received: 9 December 2023 Accepted: 24 May 2024
Published online: 06 June 2024

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