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Factors associated with delayed venous ulcer healing after endovenous intervention for superficial venous insufficiency

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ABSTRACT

Objective: This retrospective trial analyzed the effect of predetermined variables on venous ulcer healing after endovenous ablation of insufficient veins.

Methods: A total of 259 patients presenting 273 venous leg ulcers (VLUs) at Oulu University Hospital vascular outpatient clinic between January 2010 and December 2020 were included in the study. In addition to compression therapy, all patients received endovenous ablation (endothermal ablation and/or foam sclerotherapy) to promote venous healing. The hazard ratio (HR) for an ulcer to heal was analyzed in univariate analysis of predetermined factors, including age, sex, recurrent venous ulcer, presence of great saphenous vein or small saphenous vein reflux, persistent superficial vein reflux after ablation, recanalization in treated segments, ulcer age, body mass index >35 kg/m^2, history of deep vein thrombosis, history of erysipelas, ability to move, smoking, hypertension, atrial fibrillation, coronary artery disease, diabetes mellitus, and cardiac insufficiency. Logistic regression was used in a multivariate analysis to identify independent risk factors for ulcer healing.

Results: In the univariate analysis, healing was negatively associated with persistent superficial vein reflux after ablation (HR, 0.117; 95% confidence interval [CI], 0.088-0.354), recanalization in treated segments (HR, 0.161; 95% CI, 0.060-0.433), nonambulatory patient (HR, 0.322; 95% CI, 0.130-0.800), history of deep vein thrombosis (HR, 0.518; 95% CI, 0.294-0.910), and presence of small saphenous vein reflux (HR, 0.565; 95% CI, 0.384-0.830). Independent risk factors included persistent superficial vein reflux after ablation (HR, 0.123; 95% CI, 0.0051-0.295). All the patients in the persistent superficial vein reflux group had their VLUs eventually healed after further endovenous treatment.

Conclusions: When treating patients with VLUs, persistent superficial vein reflux after ablation was negatively associated with ulcer healing. After additional endovenous ablative treatment, ulcers with persistent reflux eventually healed. (J Vasc Surg Venous Lymphat Disord 2022;10:1238-44.)

Keywords: Venous ulcer; Endothermal ablation; Foam sclerotherapy

Compression therapy used to be the gold standard for venous ulcer healing. However, despite promoting venous ulcer healing, compression therapy is not very efficient, resulting in longer healing times and a high risk of recurrence.[1] In 2004, the ESCHAR study and its follow-up publications indicated that surgical treatment of varicose veins reduces the risk of ulcer recurrence.[2] Almost 15 years later, in 2018, the Early Venous Reflux Ablation (EVRA) trial showed that early endovenous ablation is beneficial for venous ulcer healing compared with delayed intervention,[3] indicating the importance of early endovenous ablation in patients with venous ulceration.

Previous articles regarding venous ulcers treated with compression therapy have noted several risk factors for delayed ulcer healing, including a larger ulcer area,[4] longer ulcer duration,[5] decreased patient mobility,[6-8] patient age,[5] and an earlier venous ulcer.[4,7,9] For now, endovenous ablation should be the standard treatment in patients with venous ulceration.[10] After superficial endovenous treatment, excluding surgery,[11] the data on how different risk factors are associated with ulcer healing is limited. In this retrospective trial, we analyzed predetermined variables for ulcer healing in patients receiving endovenous ablation (endothermal ablation and/or foam sclerotherapy) in addition to compression therapy.

METHODS

Before extracting data from the patient database, this retrospective study was approved by Northern Ostrobothnia's Ethics Committee. The study included patients presenting with venous ulcers who were treated

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at the Oulu University Hospital vascular outpatient clinic between January 2010 and December 2020. Due to the study's retrospective design, written informed consent was not obtained from the patients. To diagnose venous etiology, duplex ultrasound (DUS) was performed by a vascular outpatient physician on all patients. Superficial reflux was defined as reflux >0.5 seconds. Vein examination included evaluation of saphenous truncal veins (great saphenous vein [GSV] including its tributaries, and small saphenous vein [SSV]), major perforators, and distal tributaries. The treatment plan for superficial vein insufficiency included endothermal ablation and/or foam sclerotherapy based on the findings, with endothermal ablation planned for larger truncal veins. Patients with concurrent lower extremity arterial disease (ankle-brachial index <0.8 and need for arterial imaging and/or interventions), minor ulcers (<1 cm^2) major ulcers (diameter >25 cm), unspecified skin defects, ulcers aged >4 years, or leg ulcers with a nonvenous etiology were excluded from the study. A total of 273 venous ulcers in 259 patients (14 patients had bilateral ulcers) were finally included in this study (Fig 1). The baseline characteristics are presented in Table I. The primary treatment plan aimed to eliminate the superficial insufficiency preferably with one-step treatment, but due to the first-visit foam sclerotherapy (and scheduled endothermal ablation later) strategy in some patients, foam sclerosant limitations and recanalization effect, some patients required multiple treatments as a part of the initial therapy. Superficial insufficiency was treated regardless of diagnosed deep vein reflux. After the primary visit and treatment (foam sclerotherapy and/or endothermal ablation), patients were followed-up monthly (every 4-6 weeks) at the vascular outpatient clinic. At the follow-up visits, local wound debridement and DUS were performed, and further endovenous treatment was utilized if superficial insufficiency remained. Delayed ulcer healing was defined as poor healing (slow or no ulcer diameter reduction) after initial endovenous treatment(s), typically 2 to 4 months after the first treatment.

ARTICLE HIGHLIGHTS

- **Type of Research:** Single-center retrospective study
- **Key Findings:** This study evaluated risk factors for venous ulcer healing after endovenous ablation of superficial vein insufficiency. In multivariate analysis, persistent reflux after endovenous ablation was significantly associated with worse venous ulcer healing. Additional endovenous treatment provided healing in patients with persistent reflux.
- **Take Home Message:** Patients with prolonged venous ulcers could benefit from additional endovenous treatment when persistent reflux exists.

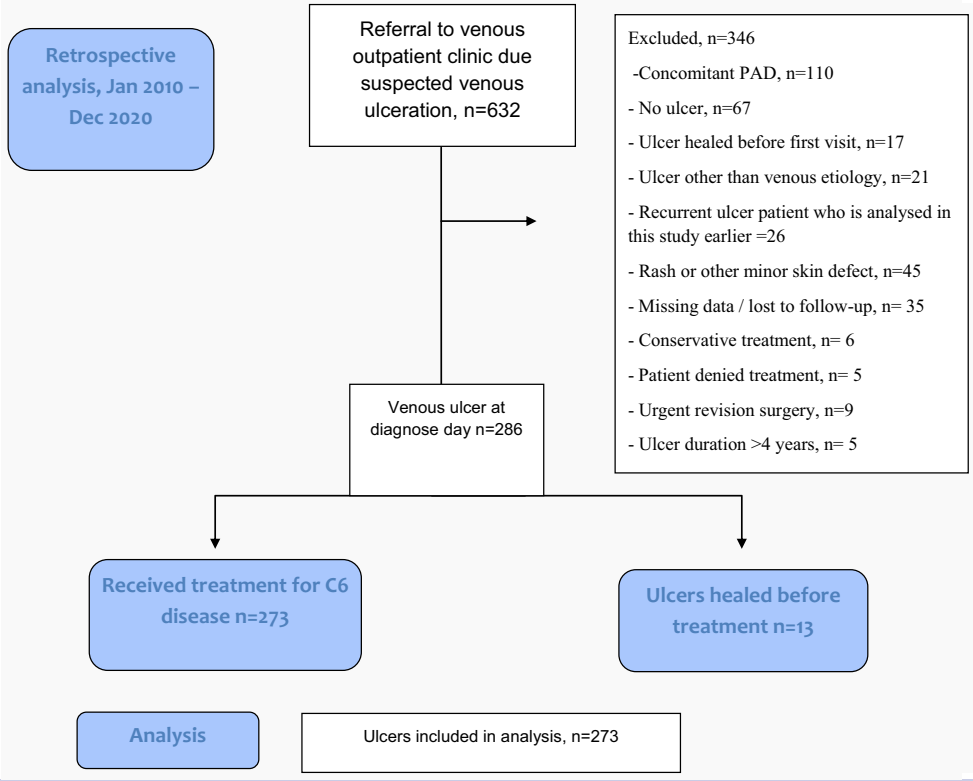

Fig 1. Flowchart of patient selection. *PAD*, Peripheral arterial disease.

Table I. Baseline characteristics of 259 patients presenting 273 ulcers

Characteristic	No. (%)
Mean age ± SD, years	71.0 ± 14.6
Female sex	153 (59.1)
Body mass index >35 kg/m^2	46 (17.8)
Comorbidities	
Hypertension	151 (57.9)
Atrial fibrillation	88 (34.0)
Coronary artery disease	31 (23.6)
Diabetes mellitus	84 (32.4)
Cardiac insufficiency	57 (22.0)
Alzheimer's/other form of dementia	21 (8.1)
History	
Admitted smoking	26 (10.0)
Earlier ulcer	39 (15.1)
Mean ulcer diameter ± SD, mm	44 ± 35
History of erysipelas	45 (17.4)
History of deep vein thrombosis	31 (12.0)
Main reflux sources[a]	
GSV	213 (82.2)
SSV	94 (36.3)
Perforant	40 (15.4)
Ulcer age, days	
<365	192 (74.1)
>365	24 (9.3)
Not known	43 (16.6)
Ability to move	
Normal	173 (66.8)
Walking with support (cane, rollator)	74 (28.6)
Nonambulatory patient (wheelchair)	12 (4.6)

GSV, Great saphenous vein; *SD*, standard deviation; *SSV*, small saphenous vein.
[a]Each patient had one or more reflux sources.

Foam sclerotherapy. Foam sclerotherapy was performed either as a single treatment modality or concomitant to endothermal ablation. Patients undergoing foam sclerotherapy were not using any analgesics or any form of anesthesia. Foam sclerotherapy was performed by utilizing Tessari's technique to prepare foam sclerosant[12] at a 1:3 sclerosant/air ratio. The sclerosant was Fibrovein 1% or 3% (Fibrovein, STD Pharmaceutical Products Ltd, Hereford, United Kingdom) depending on the caliber and location of the target vessel. With the patient lying supine, multiple intravenous cannulas (20 or 22 G) were inserted under ultrasound guidance to the locations of the varicose veins. Legs were not usually elevated during the application of foam sclerosant. A maximum of 2 mL of foam sclerosant per cannula and a maximum of 10 mL of foam sclerosant per leg were used according to European Society for Vascular Surgery guidelines.[13] The distribution of foam sclerosant was observed by DUS during the injection to prevent extravasation or excessive deep vein doses. Depending on the superficial reflux anatomy and vein calibers, the aim of using foam sclerotherapy was either to cover the whole superficial vein insufficiency, including truncal (GSV or SSV) veins, or treat distal varicosities, crural perforators, and other insufficient veins surrounding the ulcer. After the treatment, adhesive dressings were applied to puncture areas, and postoperative compression was applied with compression stockings or elastic bandages.

Endothermal ablation. Endothermal ablation was performed under local tumescent anesthesia using either a VNUS Closurefast (VNUS Medical Technologies, San Jose, CA) radiofrequency catheter or a Ceralas Biolitec endovenous laser catheter (Biomedical Technology, Jena, Germany). The catheter was introduced into the target vein under ultrasound guidance and positioned approximately 2 cm distal to the saphenofemoral or saphenopopliteal junction depending on the truncal vein. The great saphenous vein was treated from the start of the straight segment but not below 8 cm of the knee level, and the SSV was treated from the mid-calf. In case of tortuous anatomy or perforant insufficiency, an ELVeS Radial two-ring slim laser catheter (Biomedical Technology, Jena, Germany) was used, and access to the vessel was obtained with a standard 16 G intravenous cannula. The tumescent anesthesia was then applied around the vein before endothermal ablation. With the radiofrequency catheter, pre-programmed heating cycles lasting 20 seconds and a targeting catheter temperature of 120 °C were used. The cycle was usually performed twice in the first segment near the junctional area and the segments with large perforators; otherwise, the heating cycle was performed once. With endovenous laser ablation, the aim was to deliver 70 to 80 J/cm to the target vessel. As in foam sclerotherapy, postoperative compression was applied after the treatment.

Compression therapy and wound care. In addition to postoperative compression after endovenous ablation, all patients received daytime compression to promote venous ulcer healing, usually with class II (23-32 mmHg) thigh-high compression stockings. If the patient did not tolerate thigh-high compression, other options were class II knee-high compression or elastic bandaging. Between visits to the venous outpatient clinic, local wound care was organized through either the primary health care center or by homecare nurses.

Outcomes. After endovenous ablation of superficial insufficiency, the hazard ratio (HR) for a venous ulcer to heal was determined in univariate analysis of the

Table II. Univariate and multivariate analysis of wound healing

	Univariate HR	95% CI	*P*	Multivariate HR	95% CI	*P*
Age, years						
>85	1					
65-85	1.112	0.779-1.586	.56			
<65	0.992	0.617-1.377	.69			
Female sex	0.994	0.774-1.276	.96			
Recurrent ulcer	1.145	0.668-1.962	.62			
GSV reflux	1.118	0.808-1.547	.50			
SSV reflux	0.565	0.384-0.830	.004	0.712	0.462-1.098	.12
Persistent superficial vein reflux after ablation	0.117	0.088-0.354	<.001	0.123	0.0051-0.295	<.001
Recanalization in treated segments[a]	0.161	0.060-0.433	<.001	0.471	0.135-1.646	.24
Ulcer diameter >50 mm	0.810	0.611-1.074	.14			
Ulcer age, days						
<365	1.357	0.805-2.288	.25			
>365	1.261	0.553-2.874	.30			
Not recorded/not known	1					
Comorbidities						
Hypertension	0.94	0.635-1.395	.76			
Atrial fibrillation	1.016	0.681-1.514	.94			
Coronary artery disease	1.036	0.658-1.633	.88			
Diabetes mellitus	1.016	0.675-1.531	.94			
Cardiac insufficiency	0.937	0.589-1.491	.78			
History of deep vein thrombosis	0.518	0.294-0.910	.02	0.628	0.333-1.184	.15
Body mass index >35 kg/m^2	0.907	0.550-1.497	.7			
Alzheimer's/other dementia	0.814	0.404-1.642	.57			
History of erysipelas	0.851	0.513-1.413	.54			
Ability to move						
Normal	1					
Walking with support (cane, rollator)	1.158	0.755-1.777	.5			
Wheelchair	0.322	0.130-0.800	.015	0.237	0.089-0.632	.004
Smoking	0.643	0.349-1.185	.16			

CI, Confidence interval; *GSV*, great saphenous vein; *HR*, hazard ratio; *SSV*, small saphenous vein.
[a]Recanalization was noted in follow-up visits.

following parameters: age, sex, recurrent venous ulcer, presence of GSV or SSV reflux, persistent superficial vein reflux after ablation, recanalization in treated segments, ulcer age, body mass index >35 kg/m^2, history of deep vein thrombosis, history of erysipelas, ability to move, smoking, and predefined disorders (hypertension, atrial fibrillation, coronary artery disease, diabetes mellitus, and cardiac insufficiency). Furthermore, in the case of significant univariate results ($P < .05$), logistic regression was used in a multivariate analysis to identify independent risk factors for ulcer recurrence.

Statistical analysis. Summary statistics are presented as mean with standard deviation unless other stated. Fourteen patients had more than one ulcer, causing the data within a patient to be dependent, which was noticed in all analyses. The proportional hazards Cox frailty model was used when univariate and multivariate HRs for healing were calculated and 95% confidence intervals (CIs) are presented with HR. Analyses were performed using SAS (version 9.4, SAS Institute Inc, Cary, NC). Two-tailed *P*-values are presented.

RESULTS

Univariate analysis. The results of the univariate analysis are shown in Table II. In contrast to risk factors associated with delayed healing during compression therapy only, patients undergoing endovenous ablation in addition to compression therapy had no difference in ulcer healing in different age groups. Recurrent ulcers healed similarly to primary venous ulcers. In addition, ulcer age did not affect ulcer healing in the univariate analysis. History of deep vein thrombosis and disability requiring a wheelchair for movement had a negative

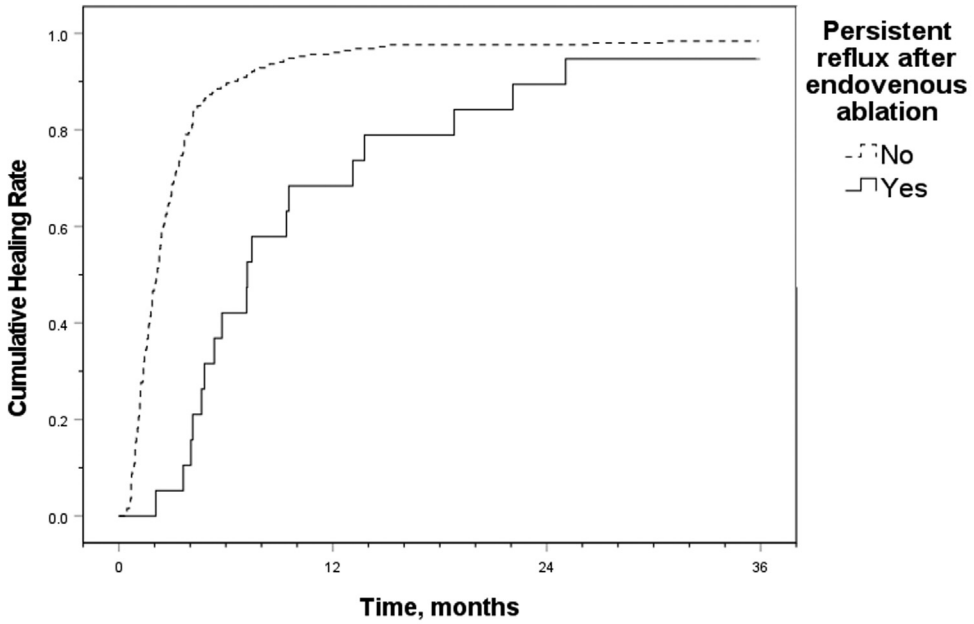

Fig 2. Cumulative ulcer healing with and without persistent superficial vein reflux. The median time to ulcer healing was 7.2 months for patients with persistent superficial vein reflux and 2.1 months for patients without persistent superficial vein reflux ($P = .0001$).

impact on ulcer healing, which confirmed earlier studies. Healing was also negatively associated with persistent superficial vein reflux after ablation, the presence of recanalization in treated segments, and the presence of SSV as a reflux source.

Multivariate analysis. The multivariate analysis with logistic regression included the presence of SSV reflux, persistent superficial vein reflux after ablation, the presence of recanalization in treated segments, history of deep vein thrombosis, and nonambulatory patients. The two variables significantly associated with delayed ulcer healing were persistent superficial vein reflux after ablation and nonambulatory patient (Table II).

Persistent superficial vein reflux and ulcer healing. Cumulative ulcer healing with and without persistent superficial vein reflux is shown in Fig 2. All patients (n = 19) with persistent reflux had their ulcers eventually healed; 16 patients showed no ulcer healing before subsequent ablation, and in three patients, ulcer was healing (diameter reduction or complete healing) before subsequent ablation. Patients with persistent superficial vein reflux had a median estimate of ulcer healing of 7.2 months compared with patients with no persistent vein reflux of 2.1 months ($P = .0001$).

DISCUSSION

The results of this trial suggest that persistent superficial vein reflux is a strong risk factor for delayed ulcer healing. The etiology of persistent reflux is multifactorial and probably related to the missed reflux segments and incomplete treatment in the previous treatment sessions. It is also possible that some reflux sources (GSV/SSV/perforant) functioning normally during the previous examination had refluent venous flow in the following visits. In the current study, all the ulcers with diagnosed persistent reflux eventually healed after additional treatment. The authors consider that the phenomenon of persistent reflux is likely to be present in other venous centers as well, although it can be difficult to identify those patients if not followed-up with DUS regularly. In light of the current study, it seems that regular follow-up leading to further endovenous treatment when superficial insufficiency remains is important. Currently, there is no clear consensus on how many times a patient with a venous leg ulcer (VLU) should visit a vascular outpatient clinic. Based on other studies, most vascular clinics seem to prefer a single-treatment approach.[14,15] However, other studies support that patients with VLUs should be controlled and treated with further endovenous ablation when necessary. Sinabulya et al[16] noted in a prospective non-randomized follow-up study (mean follow-up of 41 months) that, after endovenous laser ablation, patients with incompetent perforators or with varicose veins in the ulcer area are susceptible to ulcer recurrence. A systematic review[17] of nonhealing venous ulcers concluded that additional ablative procedures to address incompetent perforating veins and superficial reflux seem to be effective in healing persistent or recurrent venous ulcers. These articles support the findings of the current study.

In addition to persistent reflux, the presence of SSV reflux, recanalization in treated segments, and history of deep vein thrombosis were also negatively associated with ulcer healing in the univariate analysis. The negative impact of treated segment recanalization was previously reported by Lawrence et al,[18] who noted that 12% of patients with VLUs undergoing radiofrequency ablation for perforator incompetence required a second operation to achieve perforator closure and ulcer healing. The negative impact of previous deep vein thrombosis is related to post-thrombotic syndrome and deep vein reflux related to this condition, and similar findings after superficial vein intervention have been described previously in the literature.[19] Another individual factor for delayed ulcer healing was advanced disability (ie, the requirement for a wheelchair). This finding has been described previously with regard to risk factors for delayed ulcer healing in patients receiving compression therapy only and is related to constantly elevated venous pressures causing edema and other negative effects to venous ulcers due to reduced calf and ankle mobility, as well as the effects of gravity while sitting for long periods of time.[7,8]

In addition to finding negative prognostic factors, there are some findings on factors that do not affect venous ulcer healing after endovenous ablation of superficial insufficiency. In particular, the healing potential after endovenous intervention in patients with a history of VLU for more than 1 year has been described poorly in the literature.[20] In the current retrospective trial, after endovenous intervention for superficial insufficiency, there was no difference in the HR for ulcer healing between ulcer duration <1 year and ulcer duration >1 year in univariate analysis. This finding suggests that endovenous ablation could be beneficial regardless of ulcer age. Another factor that did not affect ulcer healing in the univariate analysis was patient age. This finding suggests that modern mini-invasive techniques to treat superficial reflux are also beneficial for elderly patients with VLUs.

This study had some limitations. Due to the data being retrospectively gathered, not all the parameters were obtainable for every patient (for example, the presence of deep vein reflux was not reported sufficiently). However, recent guidelines recommend treatment of incompetent superficial veins, even in the presence of deep venous incompetence.[10] Also, the number of ulcers aged >2 years was low in this study, and 35 patients were lost to follow-up or had a major lack of follow-up data. These limitations could have caused bias in the study results. Ulcers with a very large diameter (>25 cm) or ulcers requiring immediate surgical revision were excluded from this study.

CONCLUSIONS

When treating patients with VLUs, persistent superficial vein reflux after endovenous ablation was negatively associated with ulcer healing. This finding suggests that patients without proper follow-up are at risk for delayed VLU healing. After additional endovenous ablative treatment, ulcers with persistent reflux eventually healed. It seems that additional endovenous ablation is an effective method to provide venous ulcer healing when persistent reflux exists.

AUTHOR CONTRIBUTIONS

Conception and design: TP, PO, MP
Analysis and interpretation: TP, PO, MP
Data collection: TP, LV, PO, MP
Writing the article: TP, LV, PO, MP
Critical revision of the article: TP, LV, PO, MP
Final approval of the article: TP, LV, PO, MP
Statistical analysis: TP, PO, MP
Obtained funding: MP
Overall responsibility: MP

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