Safety and efficacy of outpatient endovenous laser ablation in patients 75 years and older: a propensity score-matched analysis

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Summary

AIMS OF THE STUDY: The purpose of this study was to evaluate the safety and efficacy of endovenous laser ablation (EVLA) in patients 75 years and older in an outpatient setting.

METHODS: In this multicentre retrospective study, we collected the demographic, procedural and outcome data of all consecutive patients with varicose veins class C2 to C6 undergoing EVLA of truncal and accessory saphenous veins. The primary efficacy endpoint was complete ablation of the treated veins diagnosed with duplex ultrasound at 4-week follow up. The primary safety endpoint was endothermal heat-induced thrombosis (EHIT) and deep vein thrombosis (DVT) at 4-week follow up as diagnosed by duplex ultrasound. A secondary endpoint was minor or major bleeding.

RESULTS: Between February 2009 and December 2015, a total of 829 patients were treated with EVLA of the truncal and accessory saphenous veins. Among them, 747 were <75 years old (group 1) and 82 were ≥75 years old (group 2). The primary efficacy outcome was reached in 739 patients (98.9%) in group 1 and in 80 patients (97.6%) in group 2 (odd ratio [OR] 0.43, confidence interval [CI] 0.09–2.07; p = 0.295). The number of patients with EHIT type 2 and DVT were 4 (0.5%) and 2 (0.3%), respectively, in group 1, and 2 (2.4%) and 1 (1.2%), respectively, in group 2 (OR 4.64, CI 0.83–25.75; p = 0.079 and OR 4.59, CI 0.41–51.27; p = 0.215, respectively). Minor bleeding events occurred in 36 patients (4.8%) in group 1 and 7 patients (8.9%) in group 2 (OR 1.84, CI 0.79-4.29; p = 0.155). No major bleeding occurred in either group. Propensity score-matched analysis revealed no significant difference in efficacy and safety outcomes.

CONCLUSION: EVLA performed as an outpatient procedure seems to be effective and safe in the elderly population as compared to the younger age group.

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Introduction

Varicose veins are highly prevalent in Western countries and have been estimated to occur in 25–30% of women and 10–20% of men [1, 2]. Therefore, varicose veins represent a huge socioeconomic burden. High ligation and stripping with or without phlebectomies has traditionally been the standard therapy [3]. The results of this procedure are long lasting and have been shown to improve disease-specific and general quality of life [4, 5]. Endovenous thermal ablation consisting of endovenous laser ablation (EVLA) and radiofrequency ablation (RFA) of the great and small saphenous veins (GSV, SSV) has been introduced as an alternative, minimally invasive technique for treatment of saphenous vein incompetence. The RFA catheter delivers radiofrequency energy to achieve heat-induced venous spasm and collagen shrinkage, whereas EVLA releases thermal energy to the venous wall and blood, leading to tissue damage [6]. Easy applicability and high patient satisfaction with high acceptance rates have made these procedures increasingly popular [7]. Both EVLA and RFA are performed almost exclusively in an outpatient setting under local tumescent anaesthesia. EVLA has been shown to be associated with mid-term results comparable to high ligation and stripping for up to 5 years in terms of abolition of venous reflux and absence of remaining varicose veins [8, 9]. Furthermore, EVLA is associated with higher patient acceptance, fewer complications, less postoperative pain, and earlier return to normal activities and to work [10, 11]. Accordingly, most guidelines recommend EVLA as first-line choice for treatment of truncal varicose veins. Furthermore, the outpatient EVLA treatment has been shown to be more cost effective than inpatient high ligation and stripping [12]; hence the Swiss health authorities nowadays reimburse EVLA as an outpatient treatment modality.

Since 2018, the Swiss regulatory authorities have required outpatient treatment of varicose veins to ensure reimbursement. There is an exemption for patients older than 75 years, which allows for inpatient treatment of this older patient group. However, as there is a paucity of data concerning the safety and efficacy of EVLA in patients 75 years or older, we investigated in a multicentre study whether outpatient EVLA is safe and effective in these elderly population.

Material and methods

In this retrospective study, medical data of all patients undergoing EVLA at four medical centres (University Hospital Basel, Limmattal Hospital, Vascular Institute Central Switzerland, and Vascular Centre Rapperswil) between 2009 and 2015 were reviewed in accordance with the venous reporting standard guidelines [13]. The study followed the principles outlined in the Declaration of Helsinki and was approved by the local Ethics Committee. This manuscript was prepared in compliance with the STROBE checklist [14].

All patients signed a written informed consent form before an EVLA procedure, agreeing to use of their data anonymously for publication. The Ethics Committee granted a waiver to additional formal informed consent for retrospectively reviewing charts of subjects meeting inclusion criteria. All patients who had EVLA of the great saphenous vein (GSV), accessory saphenous vein (ASV), or small saphenous vein (SSV) with a 1470-nm wavelength radial laser (ELVeS; Biolitec, Vienna, Austria; VenaCure, Angio-Dynamics, Inc, Queensbury, NY, USA) were included in this analysis. Patients were not included in the analysis if they had an endovenous ablation technique other than EVLA.

Demographic data, preoperative risk factors, vein characteristics, procedural data including concomitant phlebectomies, and outcome data including ultrasound findings and complications were assessed. All data were collected prospectively and entered into a database.

All patients were diagnosed pre-operatively with superficial venous insufficiency according to duplex ultrasound. Vein incompetence was assessed with reflux in response to manual calf compression or Valsalva manoeuvre with the patient standing and reflux was defined as evidence of reverse flow >500 ms in a vein segment [15]. The diameter of the varicose vein was 3 mm or more.

EVLA was performed by vascular specialists. Bilateral treatment was also performed. All EVLAs were performed under local tumescent anaesthesia as walk-in, walk-out procedures. No sedation was routinely given.

The GSV was cannulated percutaneously at the distal point of insufficiency under ultrasound guidance using the Seldinger technique. After insertion of the laser fibre through the sheath, the fibre tip was advanced to the sapheno-femoral or sapheno-politeal junction, positioned 1–3 cm distal to the junction with ultrasound guidance and connected to a 1470-nm radial diode laser device. Local tumescent anaesthesia (0.5 L) was prepared using 500 ml of 0.9% saline, 50 ml of 2% rapidocaine and 5 ml of 8.4% sodium bicarbonate. Local tumescent anaesthesia was then infiltrated in the perivenous space under high-resolution

ultrasound guidance. Then the position of the laser tip was again verified before activating the laser. Laser energy was then administered at 8–10 W power using a continuous mode, with a linear endovenous energy delivery (LEED) target of 50–90 J/cm. After activation the laser fibre was slowly and continuously pulled back during ablation. We did not measure the exact treatment length; however, in general, we ablated the refluxing vein segments completely from below the knee for the GSV and from the distal calf for SSV. Refluxing tributaries were removed by phlebectomy or closed with sclerotherapy during the same procedure. As a standard, concomitant phlebectomy was performed with 1- to 3-mm incisions over varicosities by using a hook (Oesch; Salzmann AG, St Gallen, Switzerland) after laser ablation. Concomitant foam sclerotherapy was performed alone or in addition to phlebectomy using up to 10 ml of 1% to 3% aethoxysklerol mixed 1:4 with air in patients with neovascularisation or tributaries of perforators.

After the treatment, the legs were wrapped in sterile absorbent bandages and in those patients who had concomitant phlebectomy, covered with a compressive cohesive bandage. After 24 to 72 hours, the patients removed the bandage and were told to wear a class 2 compression stocking during the day for at least 1 week. The patients without concomitant phlebectomy were recommended to wear a class 2 compression stockings during the day for at least 1 week. We did not monitor compliance with use of the stockings.

Any patients undergoing EVLA procedures routinely received thromboprophylaxis with rivaroxaban 10 mg/d (Bayer AG, Zurich, Switzerland) or fondaparinux 2.5 mg subcutaneously (Sanofi-Aventis, Vernier, Switzerland) for 3 to 10 days at the discretion of the operator. The first dose was immediately administered postoperatively. Routine mobilisation was encouraged for the postoperative period.

Duplex ultrasound examination was performed at 4 weeks postoperatively to assess the treated vein segment and to look for endothermal heat-induced thrombosis (EHIT) and deep vein thrombosis (DVT), with special attention paid to the sapheno-femoral or sapheno-popliteal junctions and calf muscle veins. EHIT was classified as previously described by Kabnick et al. [16]. The presence of thrombus in gastrocnemius, posterior tibial or peroneal veins was classified as calf DVT. The presence of thrombus in popliteal and femoral veins was classified as proximal DVT. Computed tomography to exclude pulmonary embolism was performed if there was a clinical suspicion.

Definition of outcome parameters

The primary efficacy endpoint of this observational study was defined as complete abolition of the treated vein with no flow as confirmed by ultrasound. Primary safety endpoints were defined as a composite of observed incidence of EHIT, DVT and pulmonary embolism and bleeding rate.

The distance of the occluded vein or thrombus in relation to the sapheno-femoral or -popliteal junction recorded during the follow-up duplex ultrasound examinations was reviewed and classified according to the Kabnick classification [16]. The secondary endpoint of major and minor bleeding was defined as follows. Major bleeding events

were defined as fatal bleeding, bleeding in critical sites such as retroperitoneal, intracranial and spinal cord bleeding, bleeding leading to operation, significant bleeding leading to a 20 g/l or greater fall in haemoglobin, or a transfusion requirement of more than two units of whole blood / red blood cells [17]. Minor bleeding events were defined as bleeding events that were not major events and required no clinical treatment, such as haematoma.

Statistical analysis

Categorical data are presented as frequency and percentage, and continuous data reported as mean and standard deviation (SD). Data that were not normally distributed are presented as median and interquartile range and were analysed by nonparametric methods. Chi-squared and Fischer's exact and Mann- Whitney U tests were used for comparisons between the two age groups (≥75 years vs <75 years). Logistic regression models were used to assess the association between efficacy outcome and age groups. Propensity score matching was applied to reduce the effect of treatment selection bias and potential confounding effect. The propensity score (PS) was calculated using a logistic regression model. The younger patient group defined as group 1 vs the elderly group defined as group 2 were matched using the nearest neighbour matching method. Average treatment effect on the treated with nearest neighbour matching method was used to analyse the outcome variables. The average treatment effect on the treated is the expected difference in potential outcomes, stratified by the covariates, among individuals who received treatment.

We defined CEAP class, total energy applied and miniphlebectomy as potential confounders and used these variables in our PS-matching analysis. The CEAP classification of chronic venous disorders is based on clinical manifestations (C), aetiological factors (E), anatomical distribution of disease (A) and underlying pathophysiologic findings (P). We did not match for total time applied because it is reflected in total energy applied. Secondly, we did not match for sclerotherapy as the number of cases was too low.

A two-sided p-value of <0.05 was considered statistically significant. Data analyses and PS matching were performed using Stata software version 10 (Stata, Inc. Stata Statistical Software Release 10, College Station, TX, USA).

Results

From February 2009 to December 2015, 829 patients were treated with EVLA of truncal varicose veins. The total study population was 74.7% female and the mean age was 55.1 ± 14.8 years. Of the total population, 747 were below 75 years old (group 1) and 82 patients were 75 years and older (group 2).

Detailed demographic characteristics for the total population and groups 1 and 2 are shown in table 1. Lesion characteristics and procedural data are given in table 2.

Group 1 included more women than group 2, but this difference was statistically not significant (74.8 vs 73.2%, p = 0.789). CEAP clinical score C2, C3 and C4 were highly prevalent in the entire population and accounted for 94.8% of all treated varicose veins. However, group 2 showed a high prevalence of stages C4, C5 and C6, in total 53.6% versus 29.3% in group 1 (p <0.001). Total energy administered for ablating the truncal veins was similar in both groups, as was application time, concomitant phlebectomy and concomitant sclerotherapy.

Table 1: Patient demographics.

Variable		Total (n = 829)	Group 1 <75 years (n = 747)	Group 2 ≥75 years (n = 82)	p-value
Female sex, n (%)		619 (74.7)	559 (74.8)	60 (73.2)	0.789
Age (years), mean (SD)		55.1 (14.8)	52.3 (12.9)	79.8 (4.0)	<0.001
CEAP classification, n (%)	C2	285 (34.4)	268 (35.9)	17 (20.7)	0.007
	C3	281 (33.9)	260 (34.8)	21 (25.6)	0.110
	C4	220 (26.5)	188 (25.2)	32 (39.0)	0.012
	C5	15 (1.8)	13 (1.7)	2 (2.4)	0.653
	C6	28 (3.4)	18 (2.4)	10 (12.2)	<0.001

SD = standard deviation

Table 2: Lesion characteristics and procedural data.

Characteristic		Total (n = 829)	Group 1 <75 years (n = 747)	Group 2 ≥75 years (n = 82)	p-value
Treated vein, n (%)	GSV right	396 (47.8)	352 (47.1)	44 (53.7)	0.295
	SSV right	92 (11.1)	78 (10.4)	14 (17.1)	0.093
	GSV left	398 (48.0)	359 (48.1)	39 (47.6)	1.0
	SSV left	62 (7.5)	53 (7.1)	9 (11.0)	0.190
	Anterior ASV right or left	13 (1.6)	12 (1.6)	1 (1.2)	1.0
	Posterior ASV right or left	2 (0.2)	2 (0.3)	0	1.0
Vein diameter (mm), mean (SD)*		7.4 (2.9)	7.5 (2.9)	6.9 (2.5)	0.143
Applied energy (J), mean (SD)		2830 (1154)	2846 (1160)	2684 (1097)	0.228
Application time (s), mean (SD)		328 (158)	331 (161)	301 (129)	0.113
Concomitant phlebectomy, n (%)		394 (47.5)	362 (48.5)	32 (39.0)	0.130
Concomitant sclerotherapy, n (%)		25 (3.0)	23 (3.1)	2 (2.4)	1.0

GSV = great saphenous vein; SSV = small saphenous vein; ASV = accessory saphenous vein; SD = standard deviation * Total n = 429, of whom n = 388 aged <75 years

Complete occlusion of the ablated varicose veins was achieved overall in 98.8% and was 98.9% in group 1 and 97.6% in group 2 (p = 0.295). Complete recanalisation of the treated veins occurred in only two patients in group 1 and none in group 2. Detailed primary safety and efficacy outcomes of all patients and by age group are given in table 3.

In the total cohort EHIT was identified in 44 patients (5.3%) and DVT in 3 (0.7%). All cases of DVT were found to be in the calf. EHIT level 1 was identified in 38 (4.6%) patients and EHIT level 2 in 6 patients (0.7%). There were no cases of EHIT level 3 and 4. The incidence of all EHIT in group 1 and group 2 was 5.3% (40/747) and 4.8% (4/82), respectively; the difference between the groups was not statistically significant. No patient in either group experienced (symptomatic) pulmonary embolism. The incidence of DVT was similar in both groups and did not show any significant difference (0.3% in group 1 vs 1.2% in group 2, p = 0.215).

PS-matched analysis using nearest neighbour matching identified 73 patients from group 1 as control. In the PS-matched analysis we found no difference in sex between the PS-matched group 1 versus group 2 (p = 0.978). For total energy and mini-phlebectomy also, there was no statistical significance between PS-matched group 1 and group 2 (p = 0.082 and p = 0.961, respectively). For the CEAP classification there was a statistical significance between PS-matched group 1 and group 2 (p <0.001) as well as for the non-matched group. As given in table 3, PS-matched analysis showed no differences for efficacy and safety outcome variables.

Overall, minor bleeding events were documented in 43 cases (5.3%) of the whole cohort and were not different between both groups (p = 0.155). There were no major bleeding events in either group 1 or group 2. No episode of fatal bleeding occurred. Infection at the puncture site needing antibiotic treatment occurred in 3 patients in group 1 (0.4%) and 1 (1.2%) in group 2 (p = 0.335, table 3). No burns of the skin occurred during EVLA treatment.

Discussion

There is in general a paucity of data in the elderly population treated for varicose veins. Thus, to close the gap the purpose of this large, retrospective multicentre study was to evaluate the safety and efficacy of EVLA in patients 75 years and older with varicose veins in an outpatient office setting in order to offer this noninvasive treatment option to all suitable patients, regardless of their age. We could demonstrate that EVLA of truncal veins in patients 75 years old and older with C2 to C6 clinical class showed a similarly good efficacy and safety compared with the younger age group.

One main difference between the two groups was the CEAP clinical class distribution. The elderly population had more advanced venous disease, with 53.6% of the procedures performed for C4–6 disease. Our results are in line with the prospective study from Hamel-Desnos et al., which showed more severe venous insufficiency in the elderly group [18].

This could suggest that vascular specialists may be more selective in providing procedures to elderly patients. And thus conservative treatment may be more frequently offered for elderly patients than for younger patients. This may also reflect a general reluctance of general practitioners to refer elderly patients to vascular specialists until they are experiencing skin changes and venous ulcers. Our database does not capture the full number of patients referred to vascular specialists; thus, it is impossible to show how many elderly patients were treated conservatively either because of prohibitive comorbidity burden or because vascular specialists were not willing to intervene for a less severe clinical stage. Another explanation is that elderly patients with stage C2/3 are less likely to be treated with EVLA on the assumption that they have a higher interventional risk due to their higher age and therefore a less positive risk-benefit ratio and with the knowledge that at C2/3 stage the main treatment goal is improvement of symptoms.

Moreover, the elderly group consisted of significantly more male than female patients. This may be explained by

Table 3: Outcome data.

Variables		Total (n = 829) n (%)	Group 1 <75 years (n = 747) n (%)	Group 2 ≥75 years (n = 82) n (%)	OR (95% CI)	p-value	PS-matched ATT	PS-matched 95% CI
EVLA-treated vein	Complete occlusion	819 (98.8)	739 (98.9)	80 (97.6)	0.43 (0.09 to 2.07)	0.295	-0.012	−0.063 to 0.039
	Partial occlusion	8 (1.0)	6 (0.8)	2 (2.4)	3.09 (0.61 to 15.55)	0.172	0.012	−0.037 to 0.061
	Complete recanalisation	2 (0.2)	2 (0.3)	0		n.a.	n.a	n.a
Highest EHIT level during follow-up	1	38 (4.6)	36 (4.8)	2 (2.4)	0.49 (0.12 to 2.09)	0.338	0.024	−0.023 to 0.071
	2	6 (0.7)	4 (0.5)	2 (2.4)	4.64 (0.83 to 25.75)	0.079	-0.085	−0.187 to 0.017
Deep vein thrombosis		3 (0.4)	2 (0.3)	1 (1.2)	4.59 (0.41 to 51.27)	0.215	0.000	−0.033 to 0.033
Paraesthesia		89 (10.7)	84 (11.2)	5 (6.1)	0.51 (0.20 to 1.30)	0.160	-0.085	−0.234 to 0.064
Infection		4 (0.5)	3 (0.4)	1 (1.2)	3.06 (0.31 to 29.78)	0.335	0.012	−0.015 to 0.039
Minor bleeding		43 (5.2)	36 (4.8)	7 (8.5)	1.84 (0.79 to 4.29)	0.155	0.012	−0.987 to 1.011

EVLA = endovenous laser ablation; EHIT = endovenous heat induced thrombosis; n.a = not applicable; CI = confidence interval; PS-matched = propensity score-matched; ATT = average treatment effect on treated

the fact that male patients did not seeking medical help earlier and waited too long owing to neglect of the disease, as shown in the epidemiological study by Rabe et al. [2].

Despite advanced age and more severe venous disease ablation of truncal varicose veins was achieved with a rate of 97.6% and was similarly effective compared with the younger age group.

We also found that overall complication rates were low, in the elderly group as well as in the younger age group. Overall, our reported EHIT and DVT rates are less than reported in other studies, where the incidence of EHIT level 2 and higher after EVLA is reported to be 6.4–7.2% [19, 20]. However, in these studies thromboprophylaxis after EVLA was not routinely administered to all patients. The reason for the low rate of EHIT and DVT in our cohort might be the consequent administration of thromboprophylaxis and the relatively long period of application (in the most part of both groups 10 days) after the procedure. The rate of EHIT and DVT in our study was comparable to the recent randomised controlled trial showing a low risk of venous thromboembolism [21].

A difference in the energy distribution between EVLA, with shorter or longer wavelengths might impact EHIT formation. With an 810-nm laser, the heat originates from a focused tip, which directs energy forwards toward the sapheno-femoral junction. Rates of EHIT have been reported to be 4% with this wavelength [22]. Our results are based on EVLA using 1470-nm wavelengths, which targets water in the vein wall instead of haemoglobin, and radial tip fibres that emit energy circumferentially (not forwards) and this might contribute to the low rate of EHIT.

EHIT management has evolved in published reports from operative thrombectomy, and later anticoagulation was introduced with or without sapheno-femoral ligation [23, 24]. Nowadays, most authors agree that treatment with low molecular weight heparin or direct acting oral anticoagulants is adequate for most cases [6, 25]. Post-EVLA EHIT type 2 and calf DVT in our study were managed with therapeutic anticoagulation with either rivaroxaban (20 mg once daily) or weight-adjusted fondaparinux (usually 7.5 mg subcutaneously once daily) until resolution on ultrasound, in accordance with the suggested treatment algorithm that Kabnick et al. introduced with his classification system [16]. We performed a check-up ultrasound in anticoagulated EHIT patienst 4–6 weeks after the diagnosis. Resolution was achieved between 4–6 weeks of therapeutic anticoagulation.

This study has several limitations. First, it is limited by its nonrandomised observational design. However, given the large number of patients and the multicentre character, potential biases should be low. A 100% matching was not possible because of multiple covariate matching. However, the mean propensity score was not different for treated patients and controls in each block. And the test of balancing property of the propensity score was satisfied. Follow-up was relatively short, and thus might overestimate success rate. Also, selection bias cannot be excluded or fully adjusted for, given that the database is a procedural data set capturing only data of patients undergoing varicose vein procedures and excluding those undergoing conservative treatment only. This fails to capture all the patients who have been seen in the clinic and denied treatment for

various reasons. Despite these limitations, this study provides valuable information of EVLA as an outpatient procedure in the elderly population given the limited data currently available. In addition, we used the propensity score approach (similar to a multivariable regression model) that can remove the effects of unmeasured or indeed unknown confounding factors.

Based on our experience, we are convinced that EVLA is effective and safe in octogenarians and even nonagenarians. However, owing to the limited number of these patients in the study such a result could not be elaborated. Despite some weaknesses of this multicentre retrospective study, it provides insight into a real-world thermal ablation practice in Switzerland. A much larger registry or a randomised clinical trial is clearly warranted to further investigate the safety and efficacy of outpatient EVLA procedures in the elderly population.

Conclusion

This is the first report on an elderly population with varicose veins treated with EVLA as an outpatient procedure in Switzerland. EVLA seems to be safe and effective in patients 75 years and older as compared to the younger patient group, despite more advanced venous disease at presentation.

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