

Randomized clinical trial of endovenous laser ablation *versus* steam ablation (LAST trial) for great saphenous varicose veins

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Background: The aim was to compare endovenous laser ablation (EVLA) and endovenous steam ablation (EVSA) for great saphenous varicose veins in a non-inferiority study.

Methods: Patients with primary great saphenous vein reflux were randomized to EVLA (940 nm) or EVSA (SVSTM). Primary outcomes were treatment success (vein obliteration) at 52 weeks, and Venous Clinical Severity Score (VCSS) at 12 weeks. Secondary outcomes were pain, satisfaction with treatment, duration of analgesia use and days lost from daily activities, changes in Aberdeen Varicose Vein Questionnaire (AVVQ) and EQ-5DTM scores after 12 weeks, and complications at 2 and 12 weeks.

Results: A total of 227 legs were treated (EVSA, 117; EVLA, 110); 36 legs treated with EVSA received a low dose and the remaining 81 a higher dose. At 1 year, the treatment success rate after high-dose EVSA was not inferior to that of EVLA: 92 (95 per cent confidence interval (c.i.) 86 to 98) *versus* 96 (92 to 100) per cent respectively. Changes in VCSS after 12 weeks were similar: -2.69 (95 per cent c.i. -2.34 to -3.04) and -2.51 (-2.10 to -2.93). AVVQ, EQ-5DTM and EQ VAS scores improved equally 12 weeks after both treatments. Patients treated with EVSA reported less postprocedural pain, fewer days of analgesia use, were more satisfied with therapy, and had a shorter convalescence. Complication rates were comparable.

Conclusion: The 1-year treatment success of high-dose EVSA was not inferior to that of EVLA. Several secondary outcomes were in favour of EVSA. Registration number NCT02046967 (<http://www.clinicaltrials.gov>).

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Introduction

In many countries endovenous thermal ablation therapies have replaced high ligation and stripping as the treatment choice for primary incompetence of saphenous veins, as they are effective, have fewer complications, cause minimal postoperative pain and have faster recovery times^{1–4}. Because all endothermal treatments are effective, attention has shifted to finding the technique with the best side-effect profile, lowest pain scores and shortest convalescence. Only a few studies have compared the outcomes between different endothermal treatments. Two studies^{5,6} showed similar occlusion rates but faster recovery after segmental radiofrequency ablation (RFA) compared with laser ablation. Several studies^{7–9} have tried to compare different endovenous laser ablation (EVLA) techniques to assess the possible advantages of higher wavelength or specific

fibre-tip design. However, these studies were not designed to compare a single variable, such as wavelength. Other parameters, such as power or fibre-tip design, also varied, making a valid comparison impossible.

The most recent innovation is endovenous steam ablation (EVSA). Its effectiveness and safety have been demonstrated in a small pilot study¹⁰, in which microscopy of treated sheep veins showed thermally induced vein damage similar to that seen after RFA. A recent non-comparative case series¹¹ of EVSA reported a 96 per cent vein obliteration rate after 12 months and favourable patient-reported outcomes. Possible advantages of this new steam procedure are: stable and relatively low temperature, easy procedure, potentially greater cost-effectiveness, low pain scores and greater patient satisfaction. EVSA uses sterile water, a natural fluid that does not have the possible disadvantage of inducing harm by generating exogenous substances¹².

Another advantage of EVSA is strict temperature regulation; the steam produced has a constant temperature of 120°C. Because the induced temperature rise is limited (similar to the temperature applied in RFA), there may be fewer treatment-related symptoms (pain and bruising) and complications than with EVLA.

The aim of the present randomized non-inferiority study was to compare anatomical success rates and patient-reported outcomes following EVLA 940 nm and EVSA for treatment of incompetent great saphenous veins (GSVs).

Methods

Three medical centres participated in this multicentre trial. Patients referred to the Erasmus MC Rotterdam, DermaPark Uden and Flebologisch Centrum Grave were screened for suitability for the LAST trial. Inclusion criteria were: age at least 18 years, informed consent, and symptomatic primary incompetence of the GSV with reflux time exceeding 0.5 s and diameter 5 mm or more (at mid-thigh level) according to duplex ultrasound (DUS) examination. Exclusion criteria were: acute deep or superficial vein thrombosis, agenesis of the deep venous system, vascular malformation or syndrome, post-thrombotic syndrome of the obstruction type, pregnancy, immobility, allergy to lidocaine and arterial insufficiency (ankle:brachial pressure index below 0.9). Consenting patients were randomized to either EVLA or EVSA, using a computerized randomization list. The legs of patients with bilateral GSV incompetence were included separately, provided that there was at least 3 months between the two treatments. The two treatments differed too much in technique (materials and typical noise of steam pulses) to achieve blinding of both the patient and the attending physician; assessors were not blinded for practical reasons. The study was approved by the Medical Ethics Committee of Erasmus MC Rotterdam (MEC-2009-269). The trial has been registered at <http://www.clinicaltrials.gov> (registration number NCT02046967).

Treatment

All treatments were performed as an outpatient using local tumescent anaesthesia (0.5 mg adrenaline (epinephrine), 4.2 mg bicarbonate and 35 mg lidocaine diluted in 500 ml saline solution). When needed, tributaries were treated with phlebectomies at least 3 months after EVLA or EVSA.

Endovenous laser ablation

EVLA was done with a 940-nm diode laser (Dornier MedTech, Wessling, Germany) using a bare fibre. In brief,

the vein was punctured under DUS guidance, preferably at the distal point of reflux or at knee level, for ease of access, with a 19-G needle¹³. A guidewire was passed through the needle up to the level of the saphenofemoral junction (SFJ). The needle was removed and a 5-Fr catheter was inserted over the guidewire. After removing the guidewire, the laser fibre was inserted and the tip positioned 1–1.5 cm distal to the SFJ. Tumescent anaesthesia was administered under DUS guidance (250–500 ml, depending on the length of treated vein). The laser fibre was withdrawn continuously (at a speed of 2 mm/s) with a power setting of 12 W, delivering approximately 60 J/cm.

Endovenous steam ablation

EVSA was performed with the Steam Vein Sclerosis (SVSTM) system (cermaVEIN, Archamps, France). Venous access was obtained by puncture with a 19-G cannula under DUS guidance. The steam ablation catheter (diameter 1.2 mm) was passed through the cannula into the vein and positioned 2–3 cm distal to the SFJ. Some 250–500 ml (depending on the length of treated vein) of tumescent anaesthesia was administered. First, two pulses of steam were delivered to dispel condensed water in the catheter. Three pulses were then delivered at the catheter tip. The catheter was withdrawn by 1 cm and 1–4 pulses per cm of vein were emitted, depending on the diameter. For the first 36 procedures the treatment protocol was to apply 1 pulse/cm in veins smaller than 7 mm, 2 pulses/cm in veins of 7–10 mm, and 3 pulses/cm in veins larger than 10 mm. With insight and after temperature experiments¹⁴, this was increased to 2, 3 and 4 pulses/cm respectively during the study.

After treatment

Following both treatments, patients were advised to wear medical elastic compression stockings for 1 week and to mobilize immediately. Prophylactic low molecular weight heparin was not administered routinely.

Outcomes assessed and follow-up protocol

Follow-up visits were scheduled at 2, 12 and 52 weeks after the initial procedure. Primary outcomes were treatment success, defined as obliteration of the GSV and/or absence of reflux (more than 0.5 s of retrograde flow) along the treated segment of the GSV, according to DUS examination at 12 and 52 weeks, and change in the Venous Clinical Severity Score (VCSS) recorded by a clinician at 12 weeks compared with the baseline score¹⁵.

Secondary outcomes were divided into patient-reported outcomes and treatment safety. Pain was assessed by

means of a visual analogue scale (VAS) and duration of painkiller use; satisfaction with treatment was measured on a VAS, and convalescence as number of days lost from work/daily activities. These were all assessed at 2 weeks after treatment. Health-related quality-of-life (HRQoL) was assessed with two questionnaires at 0 and 12 weeks: the Dutch translation of the Aberdeen Varicose Vein Questionnaire (AVVQ), which is a validated disease-specific quality-of-life questionnaire for varicose veins¹⁶, and the EQ-5DTM, a generic instrument measuring health status (<http://www.euroqol.org>). Changes in AVVQ, EQ-5DTM and EQ VAS scores were calculated as differences between scores at 12 weeks and baseline values. To evaluate treatment safety, major and minor complications were reported at 2 and 12 weeks. Major complications were: deep venous thrombosis (DVT), superficial thrombophlebitis in tributaries, nerve injury, skin burns and (sub)cutaneous infections. Minor complications were ecchymosis and hyperpigmentation, both measured as an area (cm²)¹⁷.

Statistical analysis

The obliteration rate of EVLA was assumed to be about 92 per cent after 1 year¹⁸ and was unknown for EVSA. The non-inferiority interval was set at 10 per cent with a β of 0.80 and one-sided α of 0.025. Based on these assumptions,

the number of legs needed in this study was 116 per study group.

Success rates and other categorical variables for the two treatments were compared using proportions and 95 per cent confidence intervals (c.i.), which were estimated using the Wald method, with analysis by χ^2 test. Continuous variables (such as pain scores) were distributed normally and interpreted using means, 95 per cent c.i., and independent or paired *t* test. A per-protocol analysis was carried out. The CONSORT statement for non-inferiority trials was used as a guideline for reporting the results^{19,20}.

Results

Between November 2009 and November 2011, a total of 237 legs (in 217 patients) met the eligibility criteria and were randomized to receive treatment (*Fig. 1*). Ten patients (10 legs) did not receive the allocated treatment owing to technical treatment failure (1 EVSA, 4 EVLA) or because the treatment was declined (5 EVLA). They were not included in the analysis because of the per-protocol design. A total of 227 legs were treated in 207 patients; 117 legs in 112 patients had EVSA and 110 legs in 106 patients had EVLA. Eleven patients had EVLA in one leg and EVSA in the contralateral leg, four patients had EVLA in both legs, and five patients had EVSA in both legs. For

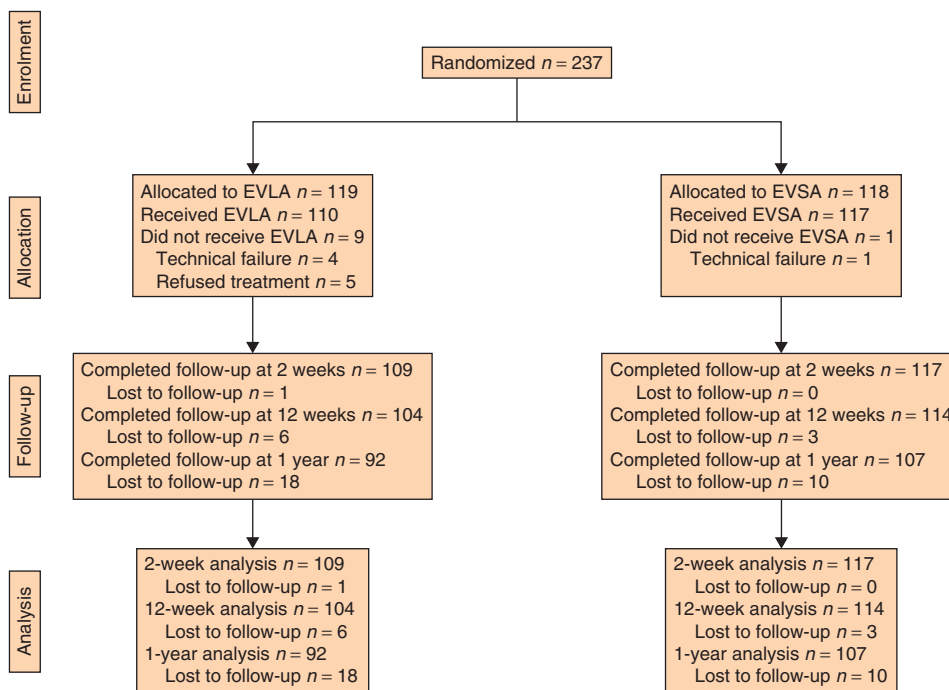


Fig. 1 CONSORT diagram for the trial. EVLA, endovenous laser ablation; EVSA, endovenous steam ablation

Table 1 Demographic data and treatment characteristics

	EVLA	EVSA (all)	<i>P</i> †	EVSA (high dose)	<i>P</i> ‡
No. of legs	110	117		81	
No. of patients	106	112			
Age (years)*	55(12)	56(13)	0.801§	55(13)	0.824§
Sex			0.185¶		0.275¶
Men					
Patients	45 (42.5)	39 (34.8)			
Legs	48 (43.6)	41 (35.0)		29 (36)	
Women					
Patients	61 (57.5)	73 (65.2)			
Legs	62 (56.4)	76 (65.0)		52 (64)	
CEAP class			0.186#		0.824#
C1	0 (0)	0 (0)		0 (0)	
C2	77 (70.0)	72 (61.5)		55 (68)	
C3	28 (25.5)	40 (34.2)		23 (28)	
C4	3 (2.7)	3 (2.6)		1 (1)	
C5	1 (0.9)	1 (0.9)		1 (1)	
C6	1 (0.9)	1 (0.9)		1 (1)	
GSV diameter (mm)			0.342#		0.535#
< 7	84 (76.4)	91 (77.8)		66 (81)	
7–10	26 (23.6)	24 (20.5)		14 (17)	
> 10	0 (0)	2 (1.7)		1 (1)	
Length of treated GSV (cm)*	32.5(6.8)	31.2(6.7)	0.172§	31.0(6.8)	0.164§
Energy*					
EVLA (J/cm)	56.6(8.1)				
EVSA (pulses per cm vein)		2.1(0.6)		2.3(0.5)	

Values in parentheses are percentages unless indicated otherwise; *values are mean(s.d.). EVLA, endovenous laser ablation; EVSA, endovenous steam ablation; CEAP, Clinical Etiologic Anatomic Pathophysiologic; GSV, great saphenous vein. †EVLA *versus* EVSA (all), ‡EVLA *versus* EVSA (high dose); §independent *t* test, ¶ χ^2 test, # χ^2 test, linear by linear association.

patients treated with EVLA, the mean(s.d.) energy delivered was 56.6(8.1) J/cm. Thirty-six patients treated with EVSA received the low dose, and the remaining 81 had the higher dose. Patients treated with EVSA received a mean(s.d.) of 2.1(0.6) pulses per cm of vein (higher dose 2.3(0.5) pulses/cm). Baseline characteristics were comparable between the treatment groups (Table 1).

Primary outcome measures: treatment success and Venous Clinical Severity Score

Table 2 summarizes the primary outcomes of the LAST trial. At 12 weeks, treatment success (obliteration of the treated GSV segment and/or absence of reflux) of all

patients who had EVSA was not inferior to that of patients who had EVLA. After 1 year, EVSA was inferior to EVLA in achieving treatment success when all patients who had EVSA were considered (86.9 per cent *versus* 96 per cent who had EVLA; $P=0.032$). Exclusion of patients who received low-dose EVSA resulted in similar success rates between EVSA and EVLA (92 *versus* 96 per cent; $P=0.331$).

Of 107 legs treated with EVSA, 84 GSVs were obliterated, nine were partially recanalized without reflux, and 14 treated GSVs were segmentally (more than 10 cm length of vein) or completely recanalized with reflux. Only four of 92 GSVs treated with EVLA were segmentally or

Table 2 Treatment success

	Anatomical success after 12 weeks*	Anatomical success after 1 year*	Change in VCSS after 12 weeks†
EVLA	101 of 104 (97.1; 93.8, 100)	88 of 92 (96; 92, 100)	-2.51 (-2.10, -2.93)
EVSA (all)	107 of 114 (93.9; 89.5, 98.3)	93 of 107 (86.9; 80.5, 93.3)	-2.90 (-2.42, -3.58)
<i>P</i> ‡	0.251¶	0.032¶	0.242#
EVSA (high dose)	76 of 78 (97; 94, 100)	68 of 74 (92; 86, 98)	-2.69 (-2.34, -3.04)
<i>P</i> §	0.896¶	0.311¶	0.279#

Values in parentheses are *percentages with 95 per cent confidence intervals (c.i.) and †95 per cent c.i. VCSS, Venous Clinical Severity Score; EVLA, endovenous laser ablation; EVSA, endovenous steam ablation. ‡EVLA *versus* EVSA (all), §EVLA *versus* EVSA (high dose); ¶ χ^2 test, #independent *t* test.

Table 3 Secondary outcome measures

	EVLA	EVSA (all)	P*	EVSA (high dose)	P†
2 weeks after intervention	n = 109	n = 116		n = 81	
Pain (VAS)	5.1 (4.7, 5.6)	2.6 (2.1, 3.1)	< 0.001	2.7 (2.1, 3.3)	< 0.001
Satisfaction (VAS)	7.7 (7.3, 8.1)	8.6 (8.3, 9.0)	0.001	8.5 (8.1, 8.9)	0.007
Duration of analgesia use (days)	3.3 (2.6, 4.1)	0.9 (0.5, 1.4)	< 0.001	1.5 (0.5, 1.8)	< 0.001
Limited in daily life (days)	4.2 (3.4, 5.0)	1.6 (1.0, 2.1)	< 0.001	1.6 (0.9, 2.3)	< 0.001
Changes in HRQoL (12 weeks after intervention versus baseline)					
AVVQ	-5.47 (-3.93, -7.01)	-5.17 (-3.63, -6.70)		-5.10 (-3.14, -7.06)	
EQ-5D™	0.039 (0.010, 0.067)	0.035 (0.011, 0.059)		0.033 (0.003, 0.062)	
EQ VAS	1.9 (0.4, 3.4)	0.8 (-0.9, 2.4)		0.0 (-2.1, 2.1)	

Values in parentheses are 95 per cent confidence intervals. EVLA, endovenous laser ablation; EVSA, endovenous steam ablation; VAS, visual analogue scale; HRQoL, health-related quality of life; AVVQ, Aberdeen Varicose Vein Questionnaire. *EVLA versus EVSA (all), †EVLA versus EVSA (high dose); all *t* test.

completely recanalized, with reflux after 1 year. In both groups, the VCSS improved by 12 weeks after treatment: -2.51 (95 per cent c.i. -2.10 to -2.93) for EVLA and -2.90 (-2.42 to -3.58) for EVSA (all patients). Changes in VCSS between baseline and 12 weeks were similar in the two groups, and there was no difference when patients who had low-dose EVSA were excluded.

Secondary outcomes

Postprocedural pain and analgesia use

Pain scores were available for 225 patients. EVSA-treated patients reported less postprocedural pain than those treated with EVLA (mean (95 per cent c.i.) VAS score 2.6 (2.1 to 3.1) versus 5.1 (4.7 to 5.6)) and a shorter duration of analgesia use (mean (95 per cent c.i.) 0.9 (0.5 to 1.4) versus 3.3 (2.6 to 4.1) days). There was no difference between the low-dose and high-dose EVSA groups (Table 3).

Satisfaction and convalescence

Patients who had EVSA were more satisfied with the therapy (mean (95 per cent c.i.) VAS score 8.6 (8.3 to 9.0) versus 7.7 (7.3 to 8.1)), and had a shorter convalescence (mean (95 per cent c.i.) 1.6 (1.0 to 2.1) versus 4.2 (3.4 to 5.0) days). The higher dose made no difference (Table 3).

Quality-of-life questionnaires

In both groups, all HRQoL outcomes improved 12 weeks after treatment, compared with scores at baseline ($P < 0.001$). Scores on the disease-specific questionnaire (AVVQ) improved substantially (by more than 30 per cent), but those on the generic questionnaires improved very little (less than 5 per cent). Changes in AVVQ, EQ-5D™ and EQ VAS scores between baseline and 12 weeks were comparable for EVSA and EVLA (Table 3).

Table 4 Complications

	EVLA	EVSA
At 2 weeks	n = 109	n = 117
Deep venous thrombosis	1 (0.9)	0 (0)
Superficial thrombophlebitis	10 (9.2)	10 (8.5)
Nerve injury	0 (0)	1 (0.9)
Skin burn	0 (0)	0 (0)
Skin infection	0 (0)	1 (0.9)
Ecchymosis (cm ²)*	4.5(13.1)	1.0(3.1)
Hyperpigmentation (cm ²)*	0.9(3.9)	0.9(4.6)
At 12 weeks	n = 98	n = 107
Superficial thrombophlebitis	0 (0)	3 (2.8)
Nerve injury	0 (0)	2 (1.9)
Ecchymosis (cm ²)*	0.0(0.4)	0.0(0.0)
Hyperpigmentation (cm ²)*	0.1(0.5)	0.3(1.8)

Values in parentheses are percentages unless indicated otherwise; *values are mean(s.d.). EVLA, endovenous laser ablation; EVSA, endovenous steam ablation.

Complications

Complications were mostly minor, and the side-effect profiles of EVSA and EVLA treatment appeared to be similar (Table 4). One patient who had EVLA developed a DVT in the common femoral vein of the treated leg 2 weeks after the intervention. Thrombophlebitis in tributaries was reported in ten legs (9.2 per cent) in the EVSA and ten (8.5 per cent) in the EVLA group 2 weeks after treatment. Three legs (2.8 per cent) in the EVSA group still had thrombophlebitis at 12 weeks. Two patients reported a sensory nerve injury 12 weeks after EVSA. Two weeks after EVLA the mean area of ecchymosis was 4.5 cm², which was larger than the mean of 1.0 cm² after EVSA.

Discussion

This trial compared EVSA with EVLA, which is the most commonly used thermal treatment for varicose veins. With the appropriate (high) dose, EVSA was not inferior to

EVLA (940 nm, bare fibre) regarding obliteration of the treated GSV segment after 1 year. The patient-reported outcomes were all in favour of EVSA: pain scores, duration of painkiller use and satisfaction with treatment. Quality of life improved similarly in both groups.

EVLA occlusion rates are usually in the range 90–95 per cent¹⁸, similar to the rate in the present study. In patients who had low-dose EVSA, the occlusion rate after 1 year was lower than that after EVLA. The initial dosing of EVSA was based on the short-term outcome of a pilot study¹⁰, in which 1 or 2 pulses/cm resulted in seven of 20 treated veins being incompletely obliterated and two having a remaining segment with reflux after 6 months. The present randomized clinical trial was initiated after the pilot study, but before an experimental study¹⁴ showing that 2 pulses/cm should be sufficient for a homogeneous temperature rise exceeding 50°C, explaining the rationale for violation of the protocol by increasing the number of pulses from at least 1 to at least 2 pulses per cm vein during the trial. The patients who received at least 2 pulses per cm vein had a success rate of 92 per cent, which is close to the 96 per cent in a recently published large case series¹¹ in which 2–4 pulses/cm were administered. Altogether, these findings suggest a clear dose–response relationship. Therefore, diameter of the veins and presence of tributaries should be taken into account when determining optimal EVSA methodology. To determine the optimal schedule for EVSA, further evaluation should be undertaken. The difficulty of designing dose-finding studies is a problem common to all endovenous thermal therapies, including EVLA for which there are numerous different laser parameters and little consensus on the optimal treatment.

In vivo measurements (temperature profile in the vein during treatment) are difficult to obtain. Ideally, these data should be investigated before setting up a randomized trial. Increasing the number of pulses per centimetre might influence the volume of tumescent anaesthesia needed for a painless procedure. However, it is unlikely to influence patient-reported outcomes at 2 weeks because the intravenous temperature rise is limited. Vein wall perforation and perivenous damage are usually responsible for side-effects of endothermal treatments; these are not found on histological examination of veins treated with EVSA¹⁰.

Of the secondary outcomes, HRQoL scores improved equally after both treatments, but the remaining patient-reported outcomes were in favour of EVSA. Reduction in pain translated into quicker recovery after EVSA, which is an important advantage from a societal perspective. The minimal clinically important difference is unknown for the HRQoL questionnaires, making it

difficult to evaluate their clinical relevance²¹. The explanation for the favourable side-effect profile may be that the peak temperature in EVSA is far lower than that of EVLA²². Peak temperatures of over 600°C at the fibre tip have been reported for EVLA, potentially leading to perforation and perivenous inflammation when the bare fibre tip is in direct contact with the vein wall^{12,23–25}. The relatively low temperature in EVSA does not seem to cause perforation of the vein wall, similar to previous findings for RFA in a bovine model²⁵. The lack of perforations after EVSA has been confirmed in experimental studies^{10,26}. In another recent experimental study²², temperature profiles of EVSA, EVLA and segmental RFA were compared. The LAST trial was performed with 940-nm bare-fibre EVLA, which was the most frequently used EVLA method when the study began. Developments in EVLA methodology aiming to improve the secondary outcomes are ongoing. Innovations in fibre-tip design (such as tulip fibre) and power administered may result in better secondary outcomes, decreasing the difference in patient-reported outcomes between EVLA and EVSA.

The gap in knowledge concerning optimal EVSA dosing is an important limitation of this study. A second limitation is that patients and practitioners were not blinded. Owing to the different materials and the typical noise that EVSA makes, blinding was impossible.

Endovenous thermal ablation is very successful for the treatment of varicose veins. The 1-year treatment success of high-dose EVSA is not inferior to that of EVLA (940 nm, bare fibre). The efficacy of EVSA might be improved by increasing the dose of the pulses, which will require formal assessment in future studies.

Disclosure

The authors declare no conflict of interest.

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