Randomized clinical trial of patient reported outcomes after endovenous 940 nm laser ablation versus 1470 nm laser ablation (COLA trial) for great saphenous vein incompetence

Wendy Malskat
Jenny Giang
Marianne de Maeseneer
Tamar Nijsten
Renate van den Bos

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ABSTRACT

Background: The independent effect of wavelength used for endovenous laser ablation (EVLA) on patient reported outcomes, health-related quality of life (HRQoL), success and complications has not yet been established in a randomized controlled trial (RCT). Our aim was to compare two different wavelengths, with identical energy level and laser fibers, in patients undergoing EVLA.

Methods: Patients with great saphenous vein (GSV) reflux were randomized into 940 nm or 1470 nm EVLA. The primary outcome was pain at one week. Secondary outcomes were satisfaction, days of analgesia use and days without normal activities at one week, HRQoL after 12 weeks, treatment success after 12 and 52 weeks, change in Venous Clinical Severity Score (VCSS) after 12 weeks and adverse events at one and 12 weeks.

Results: A total of 139 legs were treated (940 nm EVLA, 68; 1470 nm EVLA, 71). Patients in the 1470 nm EVLA group reported significantly less pain on a visual analogue scale (VAS), compared to 940 nm EVLA; median(IQR) VAS of 3(5) and 6(5) ($p = .005$) respectively. Duration of analgesia use was significantly shorter after 1470 nm EVLA; median(IQR) of 1(3) and 2(5) days ($p = 0.037$). HRQoL and VCSS improved equally in both groups. There was no difference in treatment success rates. Complications were comparable in both groups, except for more superficial vein thrombosis 1 week after 1470 nm EVLA.

Conclusion: The only difference between 940 nm and 1470 nm EVLA is the short-term patient reported tolerability one week postoperatively, with reduction of pain scores and duration of analgesia use after 1470 nm EVLA.

INTRODUCTION

Chronic venous disease (CVD) (1, 2) of the lower extremities is a very common medical condition affecting about 15% to 35% of the general population in Western countries (3, 4). More than 75% of people with CVD have incompetence of the saphenous veins of the legs (5). CVD has a great impact on patients' health-related quality of life (HRQoL), comparable to other common diseases (6).

In many countries, endovenous laser ablation (EVLA) and other endovenous thermal ablation techniques, have replaced high ligation and stripping as the first choice of treatment for incompetent saphenous veins. The efficacy of EVLA is very high (>90% obliteration rate) and the available literature shows that this success rate is observed for different laser wavelengths, power settings and pullback speeds used (7, 8). However it is less clear if the EVLA induced adverse events and tolerability of the treatment are affected by the above-mentioned laser parameters. As all EVTA treatments are highly effective, the attention in research and clinical practice has now shifted towards minimizing adverse effects by modifying laser settings, procedures and medical devices (i.e, wavelength and type of fibers). Two comparative EVLA studies demonstrated that patients treated with EVLA with higher wavelengths (1320 and 1470 nm) reported less postoperative pain, used less painkillers and were less likely to have ecchymosis than those treated with lower wavelengths (9, 10). However, in addition to the wavelength, these studies also varied in laser power or laser fiber tip, so a conclusion based on the effect of wavelength only was not possible.

The objective of the present prospective randomized controlled trial (RCT) was to assess the independent effect of EVLA wavelength (applying identical energy levels and using identical laser fibers) on patient reported outcomes (PRO), quality of life, complications and success rate.

METHODS

Consecutive patients referred to the outpatient phlebology clinic at the Department of Dermatology, Erasmus MC Rotterdam, the Netherlands, were screened for eligibility for the comparative laser or 'COLA' trial between May 2012 and November 2013, by means of medical history, clinical examination and duplex ultrasound imaging. On estimation, about half of the referred patients were diagnosed with superficial venous incompetence. The inclusion criteria for our trial were age over 18 years, symptomatic primary incompetence of the GSV with a diameter of at least 5 mm at mid-thigh level and reflux (defined as reversed flow during ≥ 0.5 seconds) according to duplex ultrasound (DUS). Exclusion criteria were pregnancy, immobility, acute deep or superficial vein thrombosis,

agenesis of the deep venous system, vascular malformation, post-thrombotic syndrome of the obstructive type, peripheral arterial disease and allergy to lidocaine. Written informed consent was obtained in all selected patients. The eligible GSVs of patients were randomly assigned to either 940 nm or 1470 nm EVLA, using a computerized randomisation list, created by an independent research nurse. In case of bilateral GSV incompetence in one patient, both legs were randomized separately.

All patients were blinded for the treatment they received. The two laser devices differed too much in device materials to achieve blinding of the attending physician. Assessors were not blinded, since the principal assessor was the attending physician performing the EVLA treatment in a large number of cases. The Medical Ethics Committee of the Erasmus MC Rotterdam approved the COLA trial (MEC-2011-455). The study was registered at www.clinicaltrials.gov (registration number NCT01637181).

Treatment

All treatments were performed in an outpatient setting under local tumescent anesthesia (0.5 mg epinephrine, 4.2 mg bicarbonate and 35 mg lidocaine diluted in 500 mL saline solution) as described previously (11). EVLA was performed either using a 940 nm Diode laser (Dornier MedTech, Wessling, Germany) or a 1470 nm Diode laser (Quanta System, SolbiateOlona, VA, Italy); for all procedures a tulip tip fiber (Tobrix, Waalre, The Netherlands) was used.

Access to the GSV was obtained by puncture with a 19 G needle under ultrasound guidance, preferably at the most distal point of reflux. A guide wire was passed through the hollow needle into the vein up to the saphenofemoral junction (SFJ). The laser fiber was inserted through a 5-Fr introducer sheath and the fiber tip was positioned at 1-2 cm distally from the SFJ. Under ultrasound guidance, 250 to 500 ml of tumescent anesthesia (depending on the length of the treated GSV) was administered into the perivenous space. After activation, the 940 nm or 1470 nm laser fiber was pulled back continuously with 2.5 mm/s using 10 W, delivering approximately 40 J/cm vein. Proebstle et al. defined a threshold for the endovenous fluence equivalent which was 6.3 J/cm per diameter vein for durable occlusion (12). Another recent experimental study (13) showed that 30 J/cm and above has proven to generate a temperature high enough for a sufficient amount of time to cause collagen denaturation needed to inflict irreversible damage to the vein wall. Concomitant phlebectomies were performed in case of presence of incompetent GSV tributaries, suitable for treatment with phlebectomy. After the procedure, patients were advised to wear thigh-high medical elastic compression stockings with at least 25-30 mm Hg at the ankle for one week and mobilize immediately. In case of bilateral GSV incompetence in the same patient, both GSVs were treated separately with a treatment interval of more than three weeks.

Outcomes assessed and follow-up protocol

Patients were scheduled for follow-up visits at 1, 12, and 52 weeks after treatment. The primary outcome was pain score, measured by means of a visual analogue scale (VAS). One week after treatment, patients had to circle a number from zero to ten, defining the maximum number of experienced pain in the week after treatment. Other patient reported outcomes, being treatment satisfaction (also measured by a VAS), number of days of analgesia use and number of days lost at work or normal daily activities were also assessed at one week post treatment. Health related quality-of-life (HRQoL) was assessed with two questionnaires at baseline and 12 weeks after treatment; the Dutch Translated Aberdeen Varicose Vein Questionnaire (AVVQ), which is a validated disease-specific quality-of-life questionnaire for varicose veins (14) and the EQ-5D™, which is a generic utility instrument measuring health status (http://www.euroqol.org). Median changes in these parameters were calculated as AVVQ, EQ-5D™ and EQ VAS scores at 12 weeks minus the baseline scores.

Secondary outcomes were treatment success, defined as obliteration of the treated segment of the GSV and/or partial obliteration of the treated GSV segment with absence of reflux, measured by DUS at 12 and 52 weeks post treatment (15), change in Venous Clinical Severity Score (VCSS), scored at baseline and 12 weeks after treatment and the occurrence of complications (deep venous thrombosis (DVT), superficial venous thrombosis (SVT) of tributaries or the distal (untreated) part of the GSV, nerve injury, skin burn, skin infection, ecchymosis and hyperpigmentation), examined at one and 12 weeks post treatment. SVT was defined as thrombus formation in a tributary of the GSV or in the distal (untreated) part of the GSV, with or without clinical signs of inflammation.

Statistical analysis

To determine a difference of 1 between the mean/median pain (VAS) scores of the treatment groups, with a SD of 2, a number of 64 legs per study arm had 80% power (one-sided alfa 0.05). Assuming a dropout of approximately 10%, the number of legs needed in this study was 71 per treatment group.

Statistical analysis was done using SPSS v. 22.0 software (SPSS Inc, Chicago, Illinois, USA). A per-protocol analysis was carried out. The primary endpoint and other continuous data were not normally distributed and therefore analyzed with non-parametric Mann-Whitney U tests. The data were presented as median with interquartile range (IQR). For the length of the treated GSV, analysis with the Independent *t*-test was used and presented as means with SD. The analysis of improvements in HRQoL scores during the study was assessed using the Wilcoxon Signed Ranks test. Patients with bilateral GSV incompetence were randomized separately for each leg. For HRQoL analysis, these patients were excluded for analysis, since patients are unable to differentiate between the impact of varicose veins of each separate leg on HRQoL.

Treatment success, adverse events and other categorical data were expressed in terms of their frequencies and percentages. The data was analyzed using the Chi-square test or, in case of low frequencies (N≤5 per cell), the Fisher exact test. All statistical tests were two-sided and p-values of <.05 were considered to be significant.

General linear regression models were used to examine the association between pain scores and type of EVLA treatment, adjusted for (higher) energy level, vein diameter, additional phlebectomies performed at baseline, complications (for instance SVT), gender and side of the treated leg, and the association of treatment success and type of EVLA treatment, adjusted for GSV diameter, energy density, SFJ incompetence and additional phlebectomies at baseline.

RESULTS

Between June 2012 and November 2013, 142 legs in 129 eligible patients were randomized to the 940 or 1470 nm EVLA (Figure 1). Three legs were excluded from the per protocol analysis because they did not receive treatment; the GSV diameter appeared to be too small in 2 legs (1 patient) and 1 leg was excluded because the guidewire could not be advanced in the GSV. A total of 139 legs were treated in 127 patients; 68 legs in 65 patients had 940 nm EVLA and 71 legs in 68 patients had 1470 nm EVLA. Twelve patients were treated bilaterally; three patients had 940 nm EVLA in both legs, three patients had 1470 nm EVLA in both legs and six patients were treated with 940 nm EVLA in one leg and 1470 nm EVLA in the contralateral leg (Table 1). Demographic data and preoperative clinical findings were comparable in the two groups (Table 1), except for the side of the treated leg; there were more left legs treated in the 1470 nm group than in 940 nm group (p = 0.023). Concomitant phlebectomies were performed in 37 (54.4%) patients of the 940 nm EVLA group and 33 (46.5%) of the 1470 nm EVLA group (p = 0.350).

Patient reported outcomes (post procedural pain, satisfaction, analgesia use and convalescence)

One week after intervention, patients treated with 1470 nm EVLA reported significantly less postoperative pain than patients treated with 940 nm EVLA (median (IQR) VAS score of 3 (5) and 6 (5) p = 0.005), and a significantly shorter duration of analgesia use(median (IQR) days of 1 (3) and 2 (5) p = 0.037; Table 2).There appeared to be no association between pain scores and (higher) energy level, vein diameter, concomitant phlebectomies performed at baseline, complications (for instance SVT) and side of the treated leg (data not shown). Only gender showed to have an association with pain; women reported higher post procedural pain scores than men (p = 0.04). There were very few outliers in administered energy levels: 5 GSVs with equal distribution between the 2 EVLA groups.

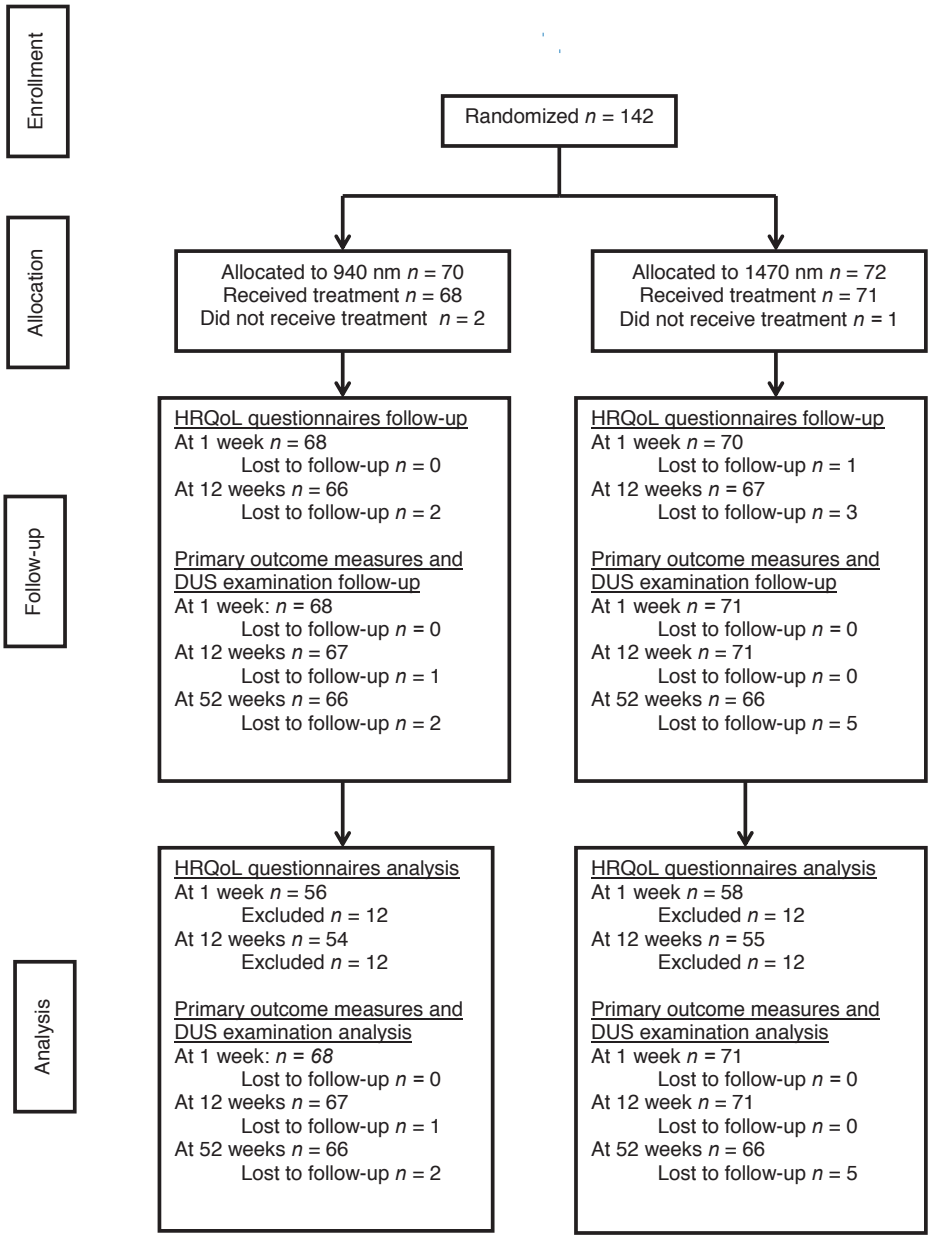

Figure 1. CONSORT diagram for the trial. HRQoL, health related quality of life; DUS, duplex ultrasound.

We performed a sensitivity analysis of the pain score including all 142 randomized limbs. For the missing values we implemented the median pain VAS of the group to which the untreated GSVs were randomized. The median pain VAS (IQR) did not change in this analysis, they remained 6.0 (5.0) and 3.0 (5.0) for 940 nm and 1470 nm EVLA respectively.

Table 1. Demographic data and preoperative clinical findings

		940-nm EVLA	1470-nm EVLA	P‡
No. of legs		70	72	
No. of patients		66	69	
Age (years)*		49.8	54.8	0.551§
Sex				
Male	patients	29 (44)	31 (45)	
	legs	29 (41)	32 (44)	
Female	patients	37 (56)	38 (55)	
	legs	41 (59)	40 (56)	
C(EAP) class				0.571¶
C1		0 (0)	0 (0)	
C2		14 (20)	15 (21)	
C3		38 (54)	41 (57)	
C4		15 (21)	14 (19)	
C5		2 (3)	2 (3)	
C6		1 (1)	0 (0)	
Side (legs)				0.019
Right		37 (53)	24 (33)	
Left		33 (47)	48 (67)	
Unilateral		56 (80)	60 (83)	0.821
Bilateral – same treatment		8 (11)	6 (8)	
Bilateral – different treatment		6 (9)	6 (8)	
GSV diameter (mm)*		33.4 (10.1)	33.1 (7.7)	.410§
Saphenofemoral junction				0.773
Competent		17 (24)	19 (26)	
Incompetent		53 (67)	53 (74)	
Length of treated GSV (cm)†		33.4 (10.1)	33.1 (7.7)	0.844#
Energy (J/cm)*		39.3 (37.8 – 41.6)	39.0 (36.7 – 40.7)	0.204§
Additional phlebectomy		39 (56)	34 (47)	0.311

Values in parentheses are percentages unless indicated otherwise; values are *median (IQR) and †mean (SD). EVLA, endovenous laser ablation; CEAP, Clinical Etiologic Anatomic Pathophysiologic; GSV, great saphenous vein. ‡Chi-square test, except §Mann-Whitney U-test, #Chi-square test, linear by linear association and #independent T-test.

Patients who had 1470 nm EVLA seemed somewhat more satisfied with the treatment, but this difference was not statistically significant (median (IQR) VAS score of 9 (2) and 8 (2) (p = 0.062)).The recovery time after treatment did not vary between both treatment groups (median (IQR) days limited in daily life 0 (2) and 0 (4) (p = 0.205)).

Quality of life

Significant improvement in AVVQ and EQ-5D™scores were seen in both groups, 12 weeks after treatment ($p < 0.001$). Changes in AVVQ, EQ-5DTM and EQ VAS between baseline and 12 weeks after treatment were comparable for 1470 nm and 940 nm EVLA (Table 2).

Table 2. Patient-reported outcomes and quality of life

	940-nm EVLA		1470 nm EVLA		
	No. of legs	**Score***	**No. of legs**	**Score***	**P‡**
1 week after intervention					
Pain (VAS)†	70	6 (3-8)	72	3 (2-7)	0.004
Satisfaction (VAS)	68	8 (7-9)	71	9 (8-10)	0.062
Duration of analgesia use (days)	68	2 (0-5)	71	1 (0-3)	0.037
Limited in daily life (days)	68	0 (0-4)	71	0 (0-2)	0.205
HRQoL at baseline					
AVVQ	56	13.38 (8.08-24.08)	58	9.37 (6.25-14.57)	0.008
EQ-5D™	56	0.843 (0.733-1.000)	58	0.843 (0.807-1.000)	0.018
EQ VAS	56	80 (61-90)	57	80 (75-90)	0.345
HRQoL 12 weeks after intervention					
AVVQ	54	7.13 (1.89-15.29)	55	4.58 (1.72-8.50)	0.047
EQ-5D™	54	1.000 (0.798-1.000)	55	1.000 (0.897-1.000)	0.017
EQ VAS	54	80 (70-85)	55	80 (80-90)	0.077
Changes in HRQoL (12 weeks *versus* baseline)					
AVVQ	54	-4.45 (-7.96 to -1.13)	55	-3.44 (-8.00 to -0.77)	0.773
EQ-5D™	54	0.034 (0-.193)	55	0.090 (0-0.157)	0.619
EQ VAS	54	0 (-5 to 10)	54	0 (-2 to 5)	0.624

*Values are median (IQR). Patients with bilateral treatment were excluded from health-related quality of life (HRQoL) analysis. †Three missing values were replaced by the median visual scale (VAS) score for each treatment group. EVLA, endovenous laser ablation; AVVQ, Aberdeen Varicose Vein Questionnaire; EQ, EuroQol. ‡Mann-Whitney U-test.

Treatment success

Treatment success was similar in 1470 nm and 940 nm EVLA groups, after 12 weeks (98.6% (95% CI 95.4 to 100) vs 98.5% (95% CI 94.7 to 100), $p = 1.00$) and after 52 weeks (93.9% (95% CI 87.7 to 98.6) vs. 90.9% (95% CI 83.3 to 97.1), $p = 0.511$; Table 3). After 52 weeks, of the 66 legs treated with 1470 nm EVLA, 61 GSV's (92.4%) were completely obliterated, 1 (1.5%) was partially recanalized without reflux and 4 (6.1%) were segmentally recanalized with reflux or completely recanalized; of the 66 legs treated with 940 nm EVLA, 55 GSV's (83.3%) were completely obliterated, 5 (7.6%) were partially recanalized without reflux and 6 (9.1%) were segmentally recanalized with reflux or completely recanalized ($p = 0.110$). There was no association between treatment success and GSV diameter or SFJ incompetence at baseline, energy density and concomitant phlebectomies.

VCSS

Twelve weeks after intervention the VCSS score had improved significantly in both the 1470 and 940 nm EVLA group, compared to baseline (p = 0.001), without difference between the two groups (Table 3).

Complications

No major adverse events occurred during this study, except for one DVT of a gastrocnemius vein in a patient of the 940 nm EVLA group 12 weeks after treatment (Table 4). One week after intervention, SVTs in tributaries or the distal (untreated) part of the GSV were more frequently seen in the 1470 nm EVLA patients(14.1% vs 4.4% (p = 0.05)). The overall side effect profile of both groups appeared to be comparable.

Table 3. Treatment success

	940-nm EVLA	1470-nm EVLA	P
Treatment success			
After 12 weeks	66 of 67 (99; 95, 100)	70 of 71 (99; 95, 100)	1.000†
After 52 weeks	60 of 66 (91; 83, 97)	62 of 66 (94; 88, 99)	0.511‡
Change in VCSS after 12 weeks*	-3 (-5 to -1) (67 legs)	-3 (-5 to -1) (69 legs)	0.883§

Values in parentheses are percentages with 95 percent CI unless indicates otherwist; values are median (IQR). EVLA, endovenous laser ablation; VCSS, Venous Clinical Severity Score. †Fisher's exact test; ‡Chi-square test; §Mann-Whitney U-test.

Table 4. Complications

	940-nm EVLA	1470-nm EVLA	P†
After 1 week	68 legs	71 legs	
Deep venous thrombosis	0 (0)	0 (0)	-
Superficial venous thrombosis	3 (4.4)	10 (14.1)	0.05‡
Nerve injury	0 (0)	0 (0)	-
Skin burn	0 (0)	0 (0)	-
Skin infection	0 (0)	1 (1.4)	0.326
Ecchymosis (cm2)*	3.82 (13.3)	7.86 (37.5)	0.668§
Hyperpigmentation (cm2)*	0.0 (0.0)	0.0 (0.0)	-
After 12 weeks	67 legs	71 legs	-
Deep venous thrombosis	1 (1.5)	0 (0)	0.486
Superficial venous thrombosis	0 (0)	2 (2.8)	0.497
Nerve injury	1 (1.5)	0 (0)	0.486
Skin burn	0 (0)	0 (0)	-
Skin infection	0 (0)	0 (0)	-
Ecchymosis (cm2)*	0.0 (0.0)	0.0 (0.0)	-
Hyperpigmentation (cm2)*	3.54 (24.6)	0.57 (3.0)	0.916§

Values in parentheses are percentages unless indicated otherwise; * values are median (IQR). EVLA, endovenous laser ablation. †Fisher's exact test, except ‡Chi-square test and §Mann-Whitney U-test.

DISCUSSION

This is the first randomized trial comparing 1470 nm and 940 nm EVLA, using identical power (10 W), energy level (40 J/cm) and laser fiber (tulip tip) and therefore solely investigating the effect of wavelength. Patients treated with 1470 nm EVLA reported significantly less pain and less duration of analgesia use one week after treatment, compared to patients with 940 nm EVLA. Improvement of HRQoL and VCSS, treatment success rates and adverse events were comparable between the two groups. Our RCT has proven that the only difference between low (940 nm) and high (1470 nm) wavelength EVLA treatment is the short-term patient reported tolerability (at one week postoperatively).

The sparse previous studies, comparing PRO's of higher EVLA wavelength to lower wavelength (9, 10), showed a benefit for the higher wavelengths by reducing postoperative pain. However these studies also varied laser parameters (laser fiber (10) and power (9)) between the groups, possibly creating confounding. Side effects after EVLA treatment, such as pain and ecchymoses, are assumed to be partly a result of vein wall perforations, due to high temperatures. In-vitro measurements have recently shown that temperature profiles of EVLA are wavelength-independent (13, 16). It is therefore unlikely that the identified difference in pain scores in the present study is due to varying temperature. Also, in both treatment groups tulip tip laser fibers were used, which are less likely to cause vein wall perforations, compared to bare fibers (17).

In experimental models, 1470 nm EVLA generate more steam bubbles than 940/980 nm EVLA, with a better temperature diffusion (12). The generated heat of 940 nm EVLA seems to diffuse less, and hence may cause more local tissue damage due to prolonged temperature elevation. Also, the absorption coefficient of 940 nm EVLA in blood is about 10 times less than 1470 nm, and about 20 times less in the vein wall (18). Theoretically, this could mean that 940 nm EVLA might be able to directly irradiate and heat up the perivenous tissue of the GSV. Anatomically, the anterior cutaneous branch of the femoral nerve lies within the saphenous compartment, close to the GSV. It is possible that patients report more pain when this sensory nerve is damaged by perivenous heat induced by the 940 nm EVLA fiber. More research on the technical elements of EVLA is needed, to better explain the results of our study.

Success rates of EVLA are usually 90-95% (7, 8) and in line with the outcomes of the COLA study. Additional phlebectomies during the EVLA treatment session did not alter these results. Complication rates were also comparable to the previous literature (19), except for may be higher SVT rates in the 1470 nm group. In the current literature, a higher frequency of SVTs has been reported after endovenous radiofrequency ablation (RFA) in one study (20), but not after 1470 nm EVLA (21), compared to 940/980 nm EVLA. In theory, it is possible that 1470 nm EVLA and RFA have a better temperature diffusion than 940 nm. The generated heat can therefore spread into the tributaries or the distal

(untreated) part of the GSV, potentially causing tissue reactions and superficial vein thrombosis.

A possible limitation of the study is the definition used for relevant difference in post-operative pain score. In the present study a difference of 1 in mean/median VAS score, was considered to be clinically relevant. The latter statement may be considered quite arbitrary, but there is no current literature available reporting on relevant differences in VAS scores. Also, in HRQoL the minimal clinically relevant difference may differ from statistically significant values. In our study though, no differences in HRQoL were detected between the two groups. Another limitation of the study is that the practitioners were not blinded. Patients, however, were blinded during the entire course of the study. Since this is the first RCT investigating the independent effect of 1470 versus 940 nm EVLA wavelength on postoperative pain scores, further research is needed with different wavelengths, fibers and technical settings to make our results generalizable to EVLA treatments with other parameters.

In conclusion, this first RCT investigating the independent effect of EVLA wavelength has shown that the only difference between 940 nm and 1470 nm EVLA is the short-term patient reported tolerability at one week postoperatively, with reduction of pain scores and duration of analgesia use in the 1470 nm EVLA group. Both EVLA treatments show similar improvements of HRQoL and VCSS, treatment success rate and post-procedural complications.

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