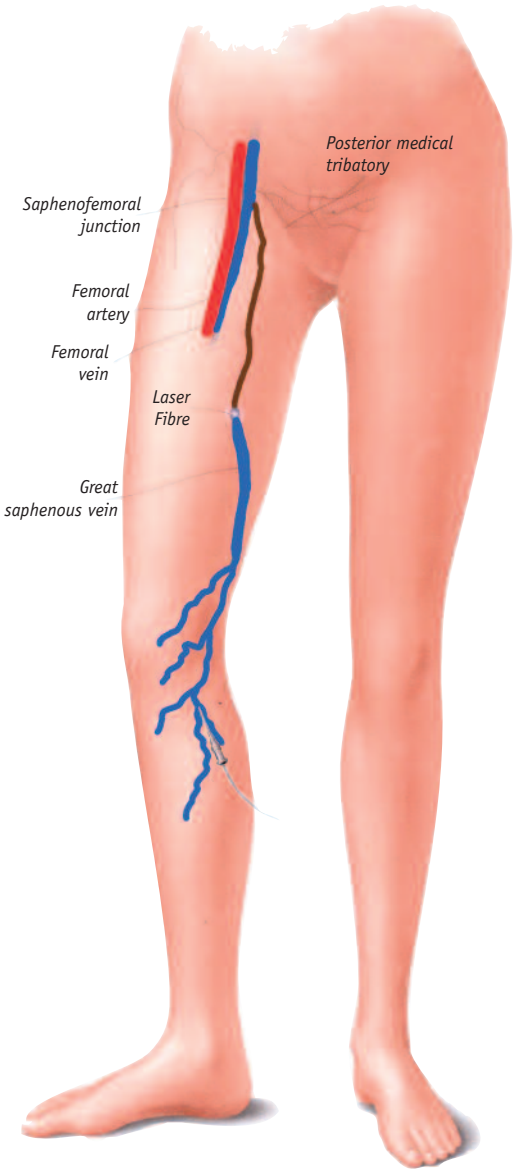
Endovenous laser therapy for varicose veins



B.C.V.M. Disselhoff

Endovenous laser therapy for varicose veins

Endoveneuze laser behandeling van varices

Proefschrift
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door

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Chapter 1

Introduction and objectives

Chapter 1 Introduction and Objectives

Varicose veins are a common problem, affecting up to 25 % of women and 15 % of men[1]. Although patients may be asymptomatic, frequent reported symptoms include cosmetic concerns, aching, heaviness, itching, and swelling, but the exact relationship between leg symptoms and varicose veins is difficult to assess[2-4.] Varicose veins also negatively affect patients quality of life, which is rectified by successful surgical treatment[5-7]. Varicose vein surgery is performed to relieve symptoms and to prevent the complications of venous disease. Successful treatment of varicose veins depends on elimination of the highest point of reflux and the elimination of the incompetent venous segment. However, the great variation in the patterns of venous reflux complicates the management of venous disease. Preoperative assessment of varicose veins has advanced from simple clinical examination to the use of hand-held Doppler and subsequently to duplex ultrasound scanning. Duplex ultrasound scanning is now accepted as the gold standard for determining venous anatomy and sites of reflux[8-12].

The majority, 70%, of varicose veins are due to saphenofemoral junction incompetence with reflux in the great saphenous vein[13-15]. The conventional treatment for varicose veins is division of the great saphenous vein and tributaries at the saphenofemoral junction and stripping of the great saphenous vein, a method described as early as 1906 by Mayo[16]. The operation is usually performed under general or conduction anaesthesia as a day-case procedure. However, surgery is accompanied by morbidity and patients require 2-3 weeks to return to normal activity[17]. Potential complications include saphenous nerve injury (4 to 25 %)[18,19], wound infection (2 to 15 %)[20], hematoma (< 30%)[21], and more rarely lymphatic damage or deep vein thrombosis(< 2 %)[20, 23]. The recurrence rates can be as high as 40% after 5 years[21-26].

With the introduction of vascular cryoprobes in 1982, cryosurgery is advocated for varicose veins because it is less traumatic to the patient, is associated with lower rates of postoperative morbidity, and has complications and recurrences rates not worse than those of traditional surgery[27,28]. Cryostripping consists of flush division of the GSV and all tributaries behind the second division, together with stripping of the GSV after catheterization with a flexible tip probe connected to a liquid nitrogen cryosurgery unit. When the probe has reached the upper calf it is chilled to – 80 degrees C; cryocoagulation occurs within about 5 seconds. With the tip kept frozen, the probe is then steadily withdrawn with manual compression of the vein below the side of coagulation. This causes disruption of the vein, which is then stripped upwards to the groin, including avulsion of the tributaries. Patients preferred cryostripping mostly because no distal incision is needed. Even though cryostripping is an improvement on conventional stripping procedures, stripping remains an invasive procedure and carries the risk of damage to surrounding tissue and wound complications.

Recently, new techniques have been introduced to ablate the GSV through a percutaneous approach. These minimally invasive techniques are based on thermal damage to the vein produced by endovenous laser ablation (EVLA) or radiofrequency ablation (RFA) and are performed without ligation of the great saphenous vein and tributaries at the saphenofemoral junction. For endovenous laser the GSV, 5 cm below the knee, is accessed under ultrasound guidance and the tip of the laser fibre is positioned 0.5–1cm below the SFJ. Under ultrasound monitoring, 250 mL of tumescent local anaesthetic (200 mL physiological saline (0.9%), 40 mL lidocaine (1%), and adrenaline (1: 100,000) neutralized with 10 mL sodium bicarbonate (8.4%)) is administered within the facial sheath of the GSV to achieve analgesia, compression of the vein, and a heat sink. In the case of spinal or general anaesthesia, 250 ml NaCl 0.9% is administered. Manual compression was applied over the GSV while 12-Watt intermittent (1 pulse on, 1pulse off) or 14-Watt continuous laser energy is delivered from 0.5–1 cm below the SFJ to the access site at a pullback rate of 0.2 cm/s. These approaches hold the promise of less invasiveness, shorter hospitality stay, better symptom relief, and superior or equal outcome compared to traditional surgery[29-31]. The RFA catheter delivers radiofrequency current to achieve heat-induced venous spasm and collagen shrinkage whereas EVLA releases laser light, both to the blood and to the venous wall. The studies described in this thesis focused on endovenous laser ablation. The reason for using laser procedures is based on the unique characteristics of laser light [32]. Laser light is produced in a small and minimally divergent beam, which makes it possible to transport energy through fibres and to apply it in a non-contact fashion. The monochromatic nature of the light can be used to target specific chromospheres in tissue, thus enabling either selectivity or homogenous distribution in a large volume. The interaction of laser light with specific tissues is dependent on the wavelength (colour) of the light (which can range from Ultra Violet to far Infra Red) and the length of the laser pulse (which can range from continuous wave to femto seconds, 10 -15). For EVLA, laser wavelengths have been selected that allow a relatively deep penetration (several millimetres) of vascular tissues, and with power levels that can increase tissue temperature to 100 °C within seconds. Typically, continuous wave Diode lasers with wavelengths in the near infrared (700 – 1500 nm) producing 10 - 30 W can be applied for this treatment. Diode lasers are new systems based on semiconductor technology. The high electrical-to-optical efficiency permits the design of compact high-power air-cooled lasers. Aluminium gallium arsenide (AlGaAs) diode lasers emit a nominal laser wavelength of 810 nm, which can be transmitted through optical fibres of high-quality quartz. This wavelength is strongly absorbed by blood and is highly scattered and with low absorption by the vein wall. As a result, most energy is converted into heat by absorption by blood directly at the tip of the fibre. Unless there is direct contact with the fibre tip, the vein wall is heated by conduction, and typically the zone of thermal necrosis is about 0.5 mm deep[29, 32].

The relative simplicity and high patient satisfaction associated with these procedures have made them increasingly popular among patients and doctors. Moreover,

the procedures can be performed in an outpatient setting using local anaesthesia. However, the safety and efficacy of these new techniques needs to be confirmed and the benefits needs to be balanced against the more expensive equipment involved in endovenous procedures. So, proper clinical and economic evaluation with adequate follow-up in a randomized trial is essential for implementing new techniques and making final recommendations about the standard of treatment.
This thesis describes the technique of endovenous laser ablation and the outcome of various series of patients with varicose veins due to reflux in the great saphenous vein, treated by endovenous laser ablation or cryostripping in a single-centre study.

Specific objectives were:

1. To investigate the mechanism of action, to describe the thermal effect of absorption of laser light by blood, to measure intravascular temperatures in ex vivo human vein segments using an intravascular thermography catheter and to study heat dissipation in a model tissue using thermal imaging techniques.
2. To outline the technique and evaluate the results of the first 100 consecutive procedures.
3. To evaluate the 2-year results of saphenofemoral ligation as adjunct to endovenous laser treatment in patients with bilateral varicose veins.
4. To compare the 2-year results of cryostripping and endovenous laser treatment in patients with reflux in the great saphenous vein.
5. To perform a costs and cost-effectiveness comparison of cryostripping versus endovenous laser treatment.
6. To describe the histological damage to the great saphenous vein below the knee following endovenous laser treatment.
7. To investigate the risk of lymphatic complications after cryostripping versus endovenous laser treatment of the great saphenous vein.

REFERENCES

1. Callam MJ. Epidemiology of varicose veins. Br J Surg 1994; 81: 167-173.
2. Bradburry AW, Evans CJ, Allan PL, Lee A, Ruckley CV, Fowkes FG. What are the symptoms of varicose veins? Edinburgh vein study cross sectional population. Survey B M J 1999; 318:353-356.
3. Bradburry AW, Evans CJ, Allan PL, Lee AJ, Ruckley CV, Fowkes FGR. The relationship between lower limb symptoms and superficial and deep venous reflux on duplex ultrasosongraphy: the Edinburgh vein study. J Vasc Surg 2000; 32:921-931.
4. London NJM, Nash R. Varicose veins. BMJ 2000; 320: 1391-1394.
5. Smith JJ, Garrat AM, Guest M et al. Evaluating and improving health related quality of life in patient with varicose veins. J Vasc Surg 1999; 30:710-719.
6. Durkin MT, Turton EP, Wijesinghe LD, Scott DJ et al. Long saphenous vein stripping and quality of life: a randomised trial. Eur j Endovasc Surg 2001; 21:545-549.
7. Mackenzie RK, Paisley A, Allan PL, Lee AJ et al. The effect of long saphenous vein stripping on quality of life. J Vas Surg 2002; 35:1197-203.
8. Wong JKF, Duncan JL, Nichols DM. Whole-leg Duplex Mapping for varicose veins: Observations on Patterns of reflux in recurrent and primary legs, with clinical correlation. Eur J Vasc EndoVasc Surg: 2003; 25: 267-275.
9. Scott DJA, Earnshaw JJ, Murie J. Duplex imaging for varicose veins. The Evidence for vascular Surgery.1st Edition, Chapter 20. Harley: Joint Vascular Research Group. Efan Publishing Ltd 2001; 125-130.
10. Mercer Kg, Scott DJA, Beridge Dc. Preoperative duplex scanning is required before all operations for primary varicose veins. Br J Surg 1998; 85:1495-1497.
11. Wills V, Moylan D Chambers J. The use of routine duplex scanning in the assessment of varicose veins. Aust N Z J Surg 1998; 68:41-44.
12. Jutley RS, Cradile I, Cross S. Preoperative assessment of primary varicose veins: a duplex study of venous incompetence. Eur J Vasc EndoVasc Surg 2002:21:370-373.
13. Sakurai T, Gupta PC, Matsushia M and Nimura Y. Correlation of the distribution of venous reflux with clinical symptoms and venous haemodynamics in primary varicose veins. B J Surg 1998; 85: 213-216.
14. Labropoulos N, Leon M, Nicolaides AN, Giannoukas AD, Volteas N, Chan P. Superficial venous insufficiency: correlation of anatomic extent of reflux with clinical symptoms and signs. J Vasc Surg 1994:20:953-958.
15. Hanrahan LM, Kechejian GJ, Cordts PR, Rodriquez AA, Araki CA, LaMorte WW et al. Patterns of venous insufficiency in patients with varicose veins. Arch Surg 1991; 126: 687-691.
16. Mayo CH. Treatment of varicose veins. Surg Gyn Obstet 1906; 2:385-388.
17. Wright AP, Berridge Dc, Scott DJ. Return to work following varicose vein surgery: influence of type of operation, employment and social status. Eur j Endovasc Surg 2006; 31:553-557.

18. Morrison C, Dalsing MC. Signs and symptoms of saphenous nerve injury after greater saphenous vein stripping: prevalence, severity and relevance for modern practice. J Vasc Surg 2003; 38:886-890.
19. Holme JB, Skajaa K, Holme K. Incidence of lesions of the saphenous nerve after partial or complete stripping of the long saphenous vein Acta Chir Scand 1990:156:145-148.
20. Sarin S, Scurr JH, Coleridge Smith PD. Stripping of the long saphenous vein in the treatment of primary varicose veins. Br J Surg 1994;81: 1455-1458.
21. Winterborn RJ, Foy C, Earnshaw JJ. Causes of varicose vein recurrence: late results of a randomized controlled clinical trial of stripping the long saphenous vein. J Vasc Surg 2004; 40(4):634-639.
22. Dwerryhouse S, Davies B, Harradine K, Earnshaw JJ. Stripping the long saphenous vein reduces the rate of re-operation for recurrent varicose veins; five-year results of a randomized trial. J Vasc Surg 1999; 29(4):589-592.
23. Rutgers PH, Kitselaar PJEHM. Randomized trial of stripping versus high ligation combined with sclerotherapy in the treatment of the incompetent greater saphenous vein Am J Surg. 1994:168:311-315
24. Jacobsen BH. The value of different forms of treatment for varicose veins. Br J Surg. 1979; 66: 182-184.
25. Munn SR, Morton JB, Macbeth WAAG. To strip or not to strip the long saphenous vein? A varicose veins trial. Br J Surg 1981:68:426-428.
26. Hammarsten J, Pederson P, Cederlund CG, Campanello. Long saphenous vein surgery for varicose veins. A long term follow-up Eur. J. Vasc. Surg. 1990; 4: 361-364.
27. Beuninger H. Cryostripping of the long saphenous vein with a percutaneous guided probe. Dermatol Surg 2001; 27:545-548.
28. Schouten R, Mollen RM, Kuipers HC. A Comparison between cryosurgery and conventional stripping in varicose vein surgery: perioperative features and complications. Ann Vasc Surg 2006; 20:306-311.
29. Min RJ, Khilnani N, Zimmet SE. Endovenous laser treatment of saphenous vein reflux: long term results. J Vasc Interv Radiol 2003; 14:991-996.
30. Proebste TM, Gül D, Lehr HA, Kargl A, Knop J. Infrequent early recanalization of greater saphenous vein after endovenous laser treatment. J Vasc Surg 2003; 38:511-516.
31. Boné C. Tratamiento endoluminal de las varices con laser de diode studio preliminary. Rev Patol Vasc. 1999; 5: 35-46.
32. R.M. Verdaasdonk. Medical applications of Lasers. In: Finlayson DM, Sinclair BD, eds. Advances in Lasers and Applications. Bristol: Institute of Physics Publishing, 181-226. 1999.

Chapter 2

Endovenous laser ablation: an experimental study on the mechanism of action

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Abstract

Objective:
The aim of this experimental study was to investigate the mechanism of action of endovenous laser ablation (EVLA) using an 810-nm diode laser.

Methods:
We compared intermittent and continuous delivery of laser energy and studied: the absorption of laser light by blood, intravascular temperatures in ex vivo human vein segments using an intravascular thermography catheter, and heat dissipation in a model tissue using the Schlieren technique.

Results:
Laser light is absorbed by blood and converted to heat leading to coagulation, vaporization and carbonization, and forming an isolating layer at the fiber tip. Laser energy is then absorbed into the isolating layer forming black patches that burned on the laser fiber.
Intravascular temperature increased rapidly above carbonization temperatures (300 ºC) after the fiber tip reached the thermocouple, stays at this temperature for a few seconds and decreased gradually to around 30 ºC 10 seconds after the fiber tip passed the thermocouple. Schlieren techniques showed that heat spread from the laser was locally distributed and closely around the laser fiber tip while heat dissipation is minimal and comparable for both exposures. Compared with intermittent exposure, continuous exposure results in more carbonization, higher mean maximum intravascular temperature (128 ± 7 versus 75 ± 4 °C), and longer-lasting temperature of 100 °C (1.2 ± 0.4 versus 0.1 ± 0.1 s).

Conclusion:
In this experimental study, application of endovenous laser shows to be dominated by carbonization at the fiber tip. Although intraluminal laser induced heat was heterogeneously distributed, with laser tip-temperatures up to 1200 ^{0}C, heat dissipation was minimal. Continuous exposure of laser light appears to be better suited in EVLA than intermittent.

Keywords:
endovenous laser ablation, blood absorption of laser light, intravascular temperature measurements and heat dissipation.

Introduction

Endovenous laser ablation for reflux in the great saphenous vein (GSV) is a safe and effective treatment for patients with varicose veins. Although occlusion of the saphenous and abolition of venous reflux occurred in 87.9-100 %[1], the procedure is not universally successful in overcoming incomplete occlusion, bruising, and pain. More knowledge of the exact mechanism of action is required, not only to understand and prevent complications but also to improve clinical results. Currently, two mechanisms of action of EVLA have been suggested. The first is indirect heating and damage of the vein wall by intravascular steam bubble generation, resulting in thrombotic occlusion of the vein[2,3]. The second involves direct heating and damage to the vein wall of an almost empty vein, resulting in shrinkage and closure of the vein[4,5]. In vivo, during an actual endovenous laser ablation, very little blood remains within the vein following delivery of tumescent anaesthesia and external manual compression. There is no “venous circulation” and in fact blood does not flow within the target vein, nor will it flow around the laser fiber/sheath after tumescent anaesthesia is delivered. However, in contrast to the vein wall, blood will be the dominant absorber of the 810 nm laser wavelength and little blood within the vein will always be present during the procedure. Laser-induced blood vessel necrosis typically involves the absorption of light by haemoglobin and the diffusion of heat through blood, vein wall, and surrounding tissue, resulting in fibrotic occlusion of the vein. Successful EVLA requires sufficient intravascular heating to produce irreversible occlusion and subsequent fibrosis of the vein without thermal damage to the adjacent tissue. Knowledge of thermal effects in and around the vein during EVLA is essential but published data are limited[6-8]. After evaluation of our first 100 procedures[9], we switched from using intermittent to continuous exposure of laser light, because we expected that the increase in deposited energy would improve the occlusion rate; however, there are no objective data to support this decision. The purpose of this study was to gain a better understanding of EVLA. To this end, we compared intermittent and continuous laser light delivery using an 810 nm diode laser and studied the blood absorption of laser light, thermal effects in a blood-filled ex vivo human vein using an intravascular thermography catheter and model tissue using close up and thermal imaging techniques. Biological effects and histological examination after EVLA performed in patients will be published separately.

Methods and materials

All experiments were performed with an 810-nm diode laser (Diomed Inc, Andover, MA, USA), a bare 600-µm laser fiber, 10-watt laser output power measured with a calibrated power meter (Fieldmaster, Coherent Inc, Santa Clara, USA), and an automatic pull-back system (Volcano, Therapeutics Inc, Laguna Hills, USA). The pull back rate for the intermittent and continuous laser delivery was 0.2 cm/s. The study protocol was approved by the regional ethics committee of the Mesos Medical Centre, Utrecht, The Netherlands.

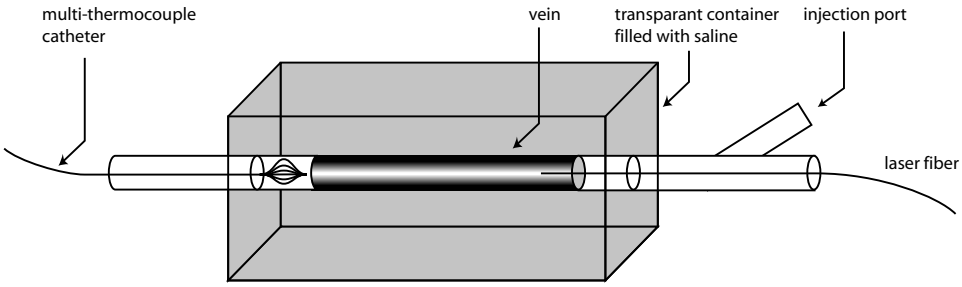


Figure 1 Experimental set-up of endovenous laser ablation.

Blood absorption of laser light

The fiber tip was fixed in an open glass cuvette and submerged in about 150 mL of heparinized whole blood. Close-up video images were recorded continuously before, during, and after exposure. We compared intermittent exposure, delivering 50, 100, and 150 J, with continuous exposure delivering 100, 200, and 300 J of laser energy. Photographic images were performed at 10, 20 and 30 s after exposure. Steam bubble generation was visualized using the experimental set-up and laser settings as described below. The volume of steam bubbles formed was assessed by measuring the increase in blood volume in a calibrated (mL) syringe tube attached to the opposite end of the plastic container. We quantified the volume of steam produced in eight human vein segments at 5, 10, 15, 20, and 25 seconds, comparing intermittent (n=4) with continuous (n=4) exposure.

Intravascular temperature measurements

EVLA was simulated (Figure 1) in human vein segments in length from 5-6 cm, placed in a plastic container filled with saline at room temperature. Saline was used to prevent desiccation of the vein and for visualization of possible perforations. A side port was attached to one side, for the injection of heparinized blood. The laser fiber was inserted into a vein segment of about 5-mm-outer diameter filled with 5 mL heparinized blood. Before each experiment, the fiber tips were freshly cut to avoid secondary thermal effects. We compared intermittent (1-s pulses with 1- s interval) and continuous exposure using equally laser fiber pull-back rates of 0.2 cm/s, resulting in the amount of energy delivered per cm vein of 25 J/cm and 50 J/cm, respectively. The great saphenous vein (GSV) was harvested from patients after a stripping procedure, flushed with hypothermic preservation solution (ViaSpan®, DuPont Pharma GmbH, Bad Homburg, Germany), and cryopreserved with 15% dimethyl sulfoxide (DMSO). After thawing, the vein was flushed with preservation solution and checked for leakage. Blood from apparently healthy male volunteers was collected in vacuum containers containing ethylenediaminetetraacetic acid (EDTA) anticoagulant and chilled. At the time of experiments the blood was allowed to warm

up to room temperature (19-21 ^{0}C). Intravascular temperature during EVLA was measured with a single-use thermography catheter using the experimental set-up described above (Figure 1). The 3.5-F thermography catheter was originally designed to measure the temperature in the coronary arteries. The catheter has a deployable 0.6-cm basket with five arms and a thermocouple on each arm, and a thermocouple in the centre of the shaft to measure temperatures up to 300 ^{0}C. The catheter was connected to a thermocouple receiver TCA-4 (Audon Electronics, Nottingham, UK). The thermocouple catheter was advanced and placed, halfway, and in the centre of the human vein. Intravascular temperatures were presented real time and were stored during endovenous laser delivery in eight human vein segments, comparing intermittent (n=4) with continuous (n=4) exposure. From the intravascular temperatures recorded by each thermocouple we calculated the mean maximum temperature; the mean maximum temperature 5 and 10 s after the laser passed the thermocouple; the time the temperature exceeded 85 ^{0}C, comparable with radiofrequency obliteration; and the time the temperature exceeded 100 ^{0}C, comparable with boiling temperature of water.

Heat dissipation

To visualize heat dissipation, we used the colour Schlieren technique, as described previously[10]. Colour Schlieren techniques are used to study dynamic processes involved in energy deposition in physiological media. This method enables the visualization of small changes in the refractive index induced by a temperature gradient in an artificial model, resulting in a pseudo-thermal image. These colour images are useful for qualitative and comparative studies. The colour shifts gradually from blue through yellow to red with increasing temperatures; however, it is not possible to assign absolute temperatures to coloured areas in images. EVLA was simulated using a tissue model composed of a transparent slab 4 x 4 cm of polyacrylamide gel in which a 3-mm diameter channel was created and filled with about 3 mL of heparinized whole blood. The polyacrylamide gel has water content comparable to that of biological tissue. Since water is the predominant conductor of thermal energy, the thermal conductivity of the gel and tissue were assumed to be approximately the same. In this way in this model, the gel model represents both the vessel wall and surrounding tissue. Video images were recorded continuously before, during, and after exposure. We performed eight in vitro experiments using the colour Schlieren technique to visualize the distribution of heat into model tissue. We compared intermittent (n=4) with continuous (n=4) exposure of laser energy.

Data collections

Data were entered into an Excel spreadsheet (Microsoft, Redmond, WA, USA). Data are presented as means ± standard deviation and percentages unless indicated otherwise.

Results

Blood absorption of laser light

Video images during laser exposure showed that laser light was absorbed by blood, resulting in the formation of a coagulum around and in front of the tip of the laser fiber. On continued laser exposure, the water in the blood started to vaporize and the vapor bubbles appeared to be incorporated into the coagulum, forming an insulating layer around the fiber. Laser light is now directly absorbed in the vapor-filled coagulum and blood started to dissociate, forming black patches in the coagulum, and burning onto the fiber tip. The changes were more extensive and occurred faster with continuous exposure (Figure 2). As control, when the laser was submerged in normal saline, laser light was not absorbed and no vapor bubbles were present. We determined the extent of carbonization after simulated EVLA. The veins were opened longitudinally to inspect the intravascular thermal damage. We observed pronounced thermal damage along the vein. Longitudinal erosions covered by a carbon layer visible at the inner surface of the vein, were confined to site of direct contact of the laser fiber (Figure 3). The tissue between the carbonized troughs showed limited or no thermal destruction.

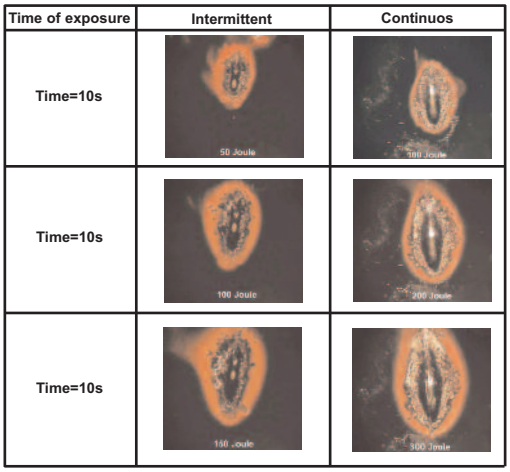


Figure 2 Photographic images of coagulum formation at the tip of the laser fiber submerged in heparinized blood at 10, 20 and 30 seconds during delivery of intermittent (50,100, and 150 J) and continuous (100, 200, and 300 J) laser energy. The changes were comparable but more extensive and occurred faster with continuous exposure.

With our experimental set-up, using vein segments filled with heparinized blood, we observed a steady generation of steam bubbles around the fiber tip. Once the bubbles achieved a certain volume, they pushed away the blood, increasing the level of blood in the connecting syringe. Steam bubble generation collapsed when the laser was switched off, but the blood level in the syringe did not drop back to the pre-irradiation level. The generation of steam required threshold energy to heat up the blood until it reached boiling temperature. The differences between the groups were in favour of continuous exposure (Table 1). We found the volume of steam produced to be 50% greater with continuous exposure (1.2 ± 0.1 mL) than with intermit-

tent exposure (0.8 ± 0.1 mL) at 25 seconds. The increase in volume of steam produced was comparable and linearly correlated with time for intermittent and continuous exposure.

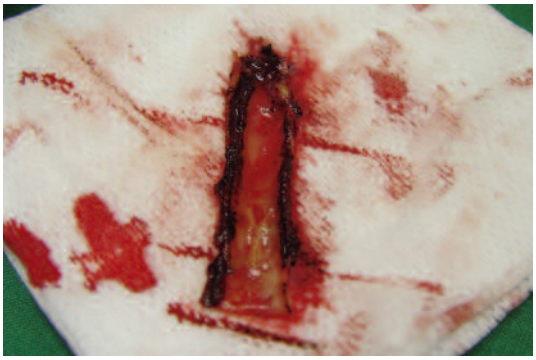


Figure 3 Human vein segment opened longitudinally showing erosions covered by a carbon layer visible at the inner surface of the vein. The tissue between the carbonized troughs showed limited or no thermal destruction.

Intravascular temperature measurement

In our experimental set-up, the thermocouples recorded variable intravascular temperatures. Laser-induced heat appeared to be locally distributed and closely concentrated around the fiber tip resulting in melting of the fiber tip. The temperature increased rapidly above carbonization temperatures (300 ºC) after the fiber tip reached the thermocouple, stays at this temperature for a few seconds and decreased gradually to around 30 ºC 10 seconds after the fiber tip passed the thermocouple (Figure 4). In all experiments the thermocouples recorded peak temperatures of 300 ºC. Away from the centre of the thermography catheter, we measured much lower temperatures ranging from 300 ºC to room temperature. Table 2 shows the mean maximum temperatures of the six thermocouples measured in 8 experiments with human vein segments filled with heparinized blood during intermittent (n=4) and continuous exposure (n=4) of laser energy. The differences between the groups were in favour of continuous exposure: 128 ± 7 (range 120-136) ^{0}C versus 75 ± 4 (range 72-80) ^{0}C. The mean maximum intravascular temperature 5 and 10 seconds after the fiber tip passed the thermocouple was 35 ± 2 (range 33-36) ºC and 30 ± 3 (range 26-33) ºC for intermittent exposure, and 45 ± 3 (range 42-50) ºC and 32 ± 3 (range 29-37) ºC for continuous exposure (Table 3). The mean time the intravascular temperature exceeded 85 ^{0}C was 0.9 ± 0.4 (range 1.5-2.4) s for intermittent exposure and 3.1 ± 0.2 (range 2.6-3.1) s for continuous exposure. The mean time the intravascular temperature exceeded 100 ^{0}C was 0.1 ± 0.1 (range 0.1-0.2) s for intermittent exposure and 1.2 ± 0.4 (range 0.7-1.5) s for continuous exposure.

Table1 Mean volume of steam produced at different exposure times, measured in 8 experiments with human vein segments filled with heparinized blood during intermittent (n=4) and continuous exposure (n=4) of laser energy.

Intermittent exposure			Continuous exposure	
Exposure	Mean volume (mL)	Laser Energy (J)	Mean volume (mL)	Laser Energy (J)
5	0.1 ± 0.1 (range 0.1-0.2)	25	0.3 ± 0.1 (range 0.2- 0.4)	50
10	0.3 ± 0.1 (range 0.2-0,4)	50	0.5 ± 0.2 (range 0.3-0,8)	100
15	0.5 ± 0.1 (range 0.4-0.6)	75	0.7 ± 0.2 (range 0.6- 1.0)	150
20	0.6 ± 0.1 (range 0.5-0.9)	100	1.0 ± 0.2 (range 0.8 -1.2)	200
25	0.8 ± 0.1 (range 0.7-0.9)	125	1.2 ± 0.1 (range1.0 -1.3)	250

Values are means ± standard deviation.

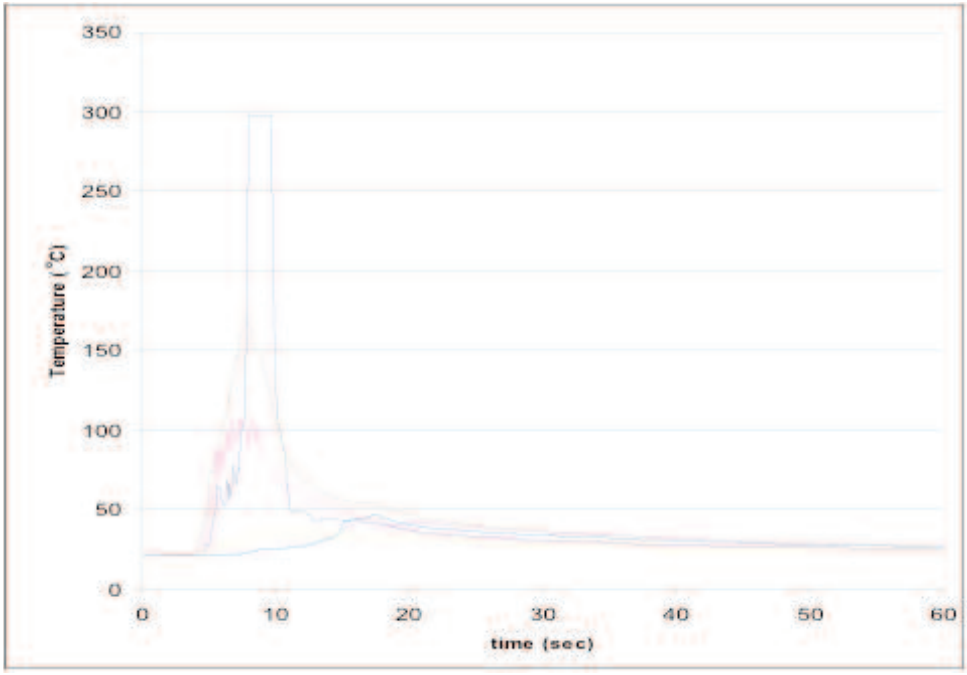


Figure 4 Intravascular temperature profile during laser fiber withdrawal, measured by the six thermocouples placed in the lumen of the vein. The temperature increased rapidly above carbonization temperatures (300 ЉC) after the fiber tip reached the thermocouple, stays at this temperature for a few seconds and decreased gradually to around 30 ЉC 10 seconds after the fiber tip passed the thermocouple

Table 2 Intravascular mean maximum temperatures, measured in 8 experiments with human vein segments filled with heparinized blood during intermittent (n=4) and continuous exposure (n=4) of laser energy.

	Intermittent exposure		**Continuous exposure**	
Human veins	Temperature (^{0}C)	J/cm	Temperature (^{0}C)	J/cm
1	80 ± 59 (range 49-128)	26	128 ± 95(range 46-298)	54
2	74 ± 31(range 42-116)	27	120 ± 32(range 50-146)	49
3	73 ± 20 (range 51-95)	23	136 ± 60(range 92-229)	50
4	72 ± 37(range 34-129)	28	127 ± 17(range 31-298)	51

Values are means ± standard deviation. J/cm, energy delivered per unit of length.

Table 3 Intravascular mean maximum temperatures, 5 and 10 seconds after onset, measured in 8 experiments with human vein segments filled with heparinized blood during intermittent (n=4) and continuous exposure (n=4) of laser energy.

	Intermittent exposure	**Continuous exposure**
Temperature (^{0}C) 5 s after onset	36 ± 8 (range 26-45)	44 ± 7 (range 33-54)
	33 ± 3 (range 31-37)	42 ± 4 (range 37-48)
	34 ± 2 (range 36-41)	50 ± 2 (range 48-52)
	36 ± 1 (range 31-42)	45 ± 2 (range 30-61)
Temperature (^{0}C) 10 s after onset	26 ± 3 (range 25-32)	37 ± 4 (range 31-43)
	30 ± 3 (range 27-36)	31 ± 1 (range 30-32)
	31 ± 4 (range 26-37)	32 ± 1 (range 31 –34)
	29 ± 2 (range 27-31)	33 ± 1 (range 31-34)

Values are means ± standard deviation. J/cm, energy delivered per unit of length.

Heat diffusion into model tissue

Figure 5 shows the temperature increase and diffusion into the tissue model, using colour Schlieren techniques. Laser-induced heat was locally distributed and closely concentrated around the fiber tip. Adjacent to the laser tip, away from the centre, the Schlieren colour changed gradually from red to yellow and blue. Colour Schlieren techniques in combination with temperature measurements showed that the mean temperature rise inside the channel of the tissue model was approximately 50 ^{0}C with intermittent exposure versus 70 ^{0}C with continuous exposure. The diffusion of heat to surrounding tissue was marginal, about 0.5 cm, and comparable for both intermittent and continuous exposure.

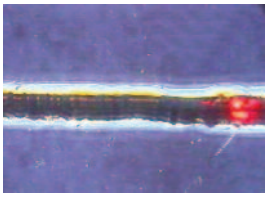
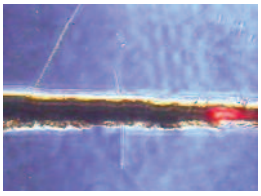
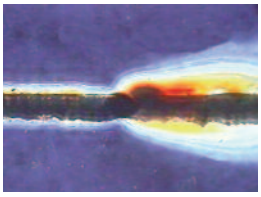
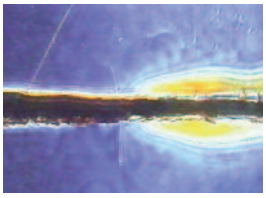
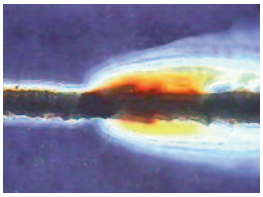
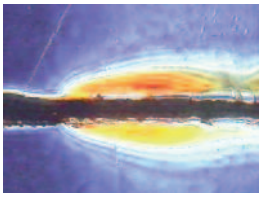
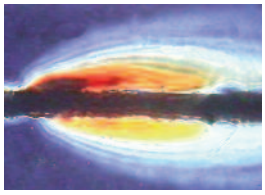
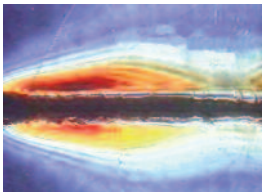
Time of exposure	Intermittent	Continuos
Time=0s		
Time=2s		
Time=5s		
Time=10s		

Figure 5 Intraluminal heat build-up and diffusion into simulated tissue model, at 0, 2, 5 and 10 seconds, visualized using colour Schlieren techniques for intermittent and continuous exposure laser exposure.

Discussion

In this experimental study, we distinguished three phases in the absorption of blood by laser light: coagulation, vaporization and carbonization. Thermally induced biochemical and morphological effects in blood have been investigated previously[11-15]. Laser light is absorbed by haemoglobin and converted into heat. At 70-80 °C, blood coagulates, forming a coagulum around and attached to the laser fiber tip. At 100 °C the water in blood vaporizes and its volume increases 1600 times in the transition to steam. These steam bubbles will be partly trapped inside the coagulum, forming an insulating layer around the fiber tip. Laser energy is directly absorbed into the vapor-filled coagulum and the temperature increases rapidly to 200-300 °C. At this temperature, blood starts to dissociate into carbon and gasses, forming black patches in the coagulum and burning onto the fiber tip (carbonization). The black carbon layer effectively absorbs laser energy and the vaporization of carbon generates bright white flashes associated with the formation of plasma (1000-2000 °C). In vivo, during an actual endovenous laser ablation, very little blood remains within the vein following delivery of tumescent anaesthesia. Any remaining blood within the vein will be vaporized. Carbonization will only occur with temperatures greater than 300 °C. The fiber tip will certainly exceed these temperatures and carbonization occurs at the fiber tip; however the carbonization in the vein walls can occur only as result of direct contact. The carbon than acts as a powerful chromophore for the laser light and once deposited onto the fiber tip into the vein wall, the process intensifies and the effectiveness of laser-induced damage to the vein walls perpetuates itself .During gross and histological examination of vein segments treated with endovenous laser we observed carbonized troughs in the vein wall (Fig 3). These areas are footprints of the laser fiber in the vein wall and are the result of direct contact between the fiber and the vein wall. We also observed that the tissue between the carbonized troughs showed limited or no thermal destruction. This finding supports that the primary mechanism of action must be direct contact between laser fiber and vein wall. If steam bubble generation was a significant factor, one would expect to see more circumferential damage or at least some more damage in the tissue between the carbonized troughs.

The formation of steam bubbles is an additional mechanism by which the vein can become damaged. We found that the volume of laser-generated steam bubbles was correlated directly with the amount of energy delivered by the laser beam, as was also described by Proebstle[2]. There is no major difference in steam bubble generation between 810-nm, 940-nm, and 980-nm diode lasers[3]. Steam formed by vaporization of blood will not exceed a temperature much higher than 110 degrees C during EVLA. Steam in excess of these temperatures would require pressures several magnitudes higher than present within the venous system during treatment. The amount of steam produced during EVLA is grossly inadequate to cause significant heat to denature collagen Type 1 and III, which is oriented circumferentially and concentrated in the adventitial layer of the vessel [16]. To our knowledge, there are no data available about intravascular temperature measurements during endovenous laser ablation. Although a 5 mm outer diameter vein segment is not representative

of the vein during endovenous ablation, in this experimental study we have to use veins in diameter of 5-6 cm because of introducing the 3.5-F thermography catheter with a deployable 0.6-cm basket with five arms and a thermocouple on each arm. The precise temperature required to cause permanent vein occlusion has not been established, but a mean vessel temperature of greater than 70 ^{0}C for several seconds is generally assumed to produce endothelial cell destruction[16,17]. Vein shrinkage is associated with the denaturation of collagen fibrils in the vein wall. Collagen has been noted to contract at about 50 ^{0}C, whereas necrosis occurs between 70 and 100 ^{0}C[16]. Corcos et al[18] showed that when permanent occlusion was observed, the endothelium and intima were always damaged. We recorded large variations of intravenous temperatures during EVLA. We found that the fiber tip melted during EVLA, which shows that the temperature at the fiber tip was at least 1200 ^{0}C, the melting temperature of glass. Three mm away from the centre of the thermography catheter, we measured minimal temperatures rise and temperatures up to 300 ^{0}C. Fiber tip temperatures exceeding 1000 ^{0}C have been described previously. Weiss [6] measured the temperature in goat veins (mean diameter 15.1 mm) during laser treatment (810-nm diode laser, 12-watt laser output, pulse time 1 s and pulse duration 1s) by using an array of five thermocouples. The highest average temperature (719 ^{0}C) was recorded at the laser tip, and temperatures of 307 ^{0}C and 231 ^{0}C were recorded 2 mm distal and 2 mm proximal to the tip. We observed that the temperature increased rapidly above carbonization temperatures (300 ºC) after the fiber tip reached the thermocouple, stays at this temperature for a few seconds and decreased gradually to around 30 ºC 10 seconds after the fiber tip passed the thermocouple (Figure 4). The slow decrease in temperature could be due to the absence of blood flow and dilatation of the vein. In vivo, blood perfusion and vasodilatation effectively transport heat away from the irradiated area[15]. Theoretically, the depth of penetration of a 810-nm diode laser beam into tissue is approximately 0.3 mm. Skin burns and permanent nerve damage have not yet seen published with EVLA, in contrast to radiofrequency obliteration. We observed that the diffusion of heat into surrounding “tissue” was minimal and comparable for intermittent and continuous delivery of laser energy. Adjacent to the fiber tip going away from the centre the colour shift gradually from approximately 100 °C (red) to 30 °C (blue). Zimmet and Min [6] measured temperature at the outer vein wall in a pig ear and concluded that peak temperatures lower than 50 °C are unlikely to cause permanent damage to perivenous tissues. Beale et al[7] measured temperature in 12 patients undergoing EVLA. The maximum recorded temperature 3, 5, and 10 mm from the GSV was 43.3°C, 42.0°C, and 36.0°C. The peak temperature was lower if perivenous infiltration was used6. So, despite the high temperatures generated during EVLA, our results suggest that transmission of heat into the surrounding tissue is minimal. Compared with intermittent exposure, continuous exposure appears to be better suited for EVLA. Most patients will develop, temporary, postoperative bruising due to vein perforations and the administration of anesthesia by perivenous infiltrations. Goldman et al [19] reported on intermittent pulse versus continuous treatment using the 810 nm diode laser. The percentage of perforations was comparable for both modes (intermittent 25.0%

and continuous 26.7%). Min et al [20] have reported on the safety and efficacy of continuous mode in EVLA. Non-entry bruising was noted in 29% of the limbs at 1 week follow-up. The degree of bruising or the absence of bruising did not relate with the degree of patients discomfort. In an animal model, using jugular veins, immediate findings showed 100 % vein perforations by histological examination[5]. However, in an effort to prevent vessel wall perforation, and hence post-procedural bruising, Goldman et al[21] found a 1320-nm continuous laser with automatic catheter withdrawal to be better suited for saphenous vein obliteration than other laser wavelengths. Kabnick et al[22] reported on the outcome of different endovenous laser wavelengths. At 1 week after the procedure bruising scores were significant different: 1.55 for 980 nm wavelength and 2.40 for 810 nm wavelength. Mordon et al [23] found in a mathematical model that less amount of energy is required in pulsed mode than in continuous mode to obtain permanent damage. However, the pulsed mode requires a very precise positioning of the laser fiber and the duration treatment is longer. Although the fact that differences between intermittent and continuous delivery of exposure of laser light during EVLA are of interest, both schedules are in successfully daily use in clinical practice.

Limitations

We did not investigate the influence of different pullback velocities or secondary effects, such as the inflammatory response, which might underlie the gradual development of vascular occlusion in the days and weeks after treatment. Our experimental set up does not allow the use of perivenous infiltration and external manual compression to reduce vein diameter and blood volume as it is done during EVLA performed in patients. Lastly, this is a static model and no blood is circulating through the vein.

Conclusion

In this experimental study, we observed three phases in the blood absorption of laser light: coagulation, vaporization and carbonization. Although laser induced heat was heterogeneously distributed with temperatures up to 1200 ^{0}C at the laser fiber tip, heat dissipation into surroundings is minimal. Continuous exposure of laser light appears to be better suited in EVLA than intermittent. It is our opinion that laser light absorption by blood results in temperatures high enough to cause sufficient vein wall damage but given the shape of the vein, the use of perivenous infiltration, and external manual compression during the actual procedure the fiber tip is more likely to make contact with the vein wall rather than be positioned in the centre of the vein. So, the pathophysiological mechanism of EVLA seems to be a dominated by vein wall absorption of laser light.

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References

1. Mundy L, Merlin TL, Fitridge RA, Hiller JE. Systematic review of endovenous laser treatment for varicose veins. BJS 2005; 92:1189-1194.
2. Proebstle TM, Lehr HA, Kargl A, Espinola, Klein C, Rother W, Berthge S et al. Endovenous treatment of the greater saphenous vein with a 940-nm diode laser: thrombotic occlusion after endoluminal thermal damage by laser generated steam bubbles J. Vasc.Surg 2002; 35(4):729-736.
3. Proebstle TM, Sandhofer M, Kargl A, Gul D, Rother W, Knop J et al. Thermal damage of the inner vein wall during endovenous laser treatment: key role of energy absorption by intravascular blood. Dermatol. Surg 2002; 28(7):596-600.
4. Min RJ, Khilnani N, Zimmet SE. Endovenous laser treatment of saphenous vein reflux: long term results. J Vasc Interv Radiol. 2003; 14:991-996.
5. Min TJ, Khilmani NM. Endovenous laser ablation of varicose veins. J Cardiovasc Surg 2005;46:395-405.
6. Weiss RA. Comparison of endovenous radiofrequency versus 810 nm diode occlusion of large veins in animal model. Dermatol Surg 2002; 28(1):56-61.
7. Zimmet SE, Min RJ. Changes in perivenous tissue during endovenous laser treatment in a swine model. J Vasc Interv Radiol 2003; 14:911-915.
8. Beale RJ, Mavor AIDF, Gough MJ. Heat dissipation during endovenous laser treatment of varicose veins: is there a risk of nerve damage. Phlebology 2006;21(1):32-35.
9. B.C. Disselhoff, D.J. der Kinderen. F.L. Moll. Is there recanalization of the great saphenous vein2 years after endovenous laser treatment?. JEVT. 2005; 12:731-738.
10. R.M. Verdaasdonk, van Swol CF, Grimbergen MC, A.I. Rem. Imaging techniques for research and education of thermal and mechanical interactions of lasers with biological and model tissues. J Biomed Opt, 2006 Jul-Aug;11(4):041110.
11. Pfefer TJ, Choi B, Vargas G, et al. Pulse laser induced thermal damage in whole blood. Trans ASME 2000;122: 196-202.
12. Barton JK, Popok D, Black JF. Thermal analysis of blood undergoing laser photocoagulation. IEEE J Sel Topics Quant Electron 2001; 7:936-943
13. Black JF, Wade N, Barton JK. Mechanistic comparison of blood undergoing laser photocoagulation at 532 and 1,064 nm. Lasers Surg Med 2005; 36:155-165.
14. Black JF, Barton JK. Chemical and structural changes in blood undergoing laser photocoagulation. Photochem Photbiol 2004; 80:89-97.
15. R.M. Verdaasdonk. Medical applications of Lasers. In: Finlayson DM, Sinclair BD, eds. Advances in Lasers and Applications. Bristol: Institute of Physics Publishing, 181-226. 1999.

16. Gorisch W, Boergen KP. Heat induced contraction of blood vessels. Lasers Surg Med 1982; 2:11-13.
17. De Boer JF, Lucassen GW, Verkruysse W et al. Thermolysis of port wine vessels: diameter of a damaged blood vessel depends on the laser pulse length. Lasers Surg Med. 1996; 11:117-180.
18. Corcos L, Dini S, De Anna D, Marangoni O et al. The immediate effects endovenous diode 808 nm laser in the great saphenous: morphology study and clinical implications. J Vasc Surg 2005;41(6):1018-1024.
19. Goldman MP, Iyer S. Endoluminal closure of the great saphenous vein with the 810nm Diomed laser: intermittent pulse versus continuous treatment. 2002 ACP Congress, Florida, USA.
20. Min R. endovenous laser treatment using continuous mode. 2002 ACP Congress, Florida.
21. Goldman MP, Maurico M, Rao J. Intravascular 1320-nm Laser closure of the great saphenous vein: a 6-to12-month follow-up study. Dermatol Surg 2004; 30:1380-1385.
22. Kabnick LS. Outcome of different endovenous laser wavelengths for great saphenous vein ablation. J Vasc Surg 2006;43:88-93.
23. Mordon SR, Wassmer B, Zemmouri J. Mathematical modelling of endovenous laser treatment. Biomed Eng Online 2006; 25:5-26.

Chapter 3

Is there recanalization of the great saphenous vein 2 years after endovenous laser treatment?

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Purpose:
To report the 2-year single-center results of endovenous laser treatment (EVLA) for reflux in the great saphenous vein (GSV).

Methods:
From January 2002 to January 2003, 85 symptomatic patients (56 women; mean age 49 years, range 27-80) underwent EVLA in 100 limbs. All patients were symptomatic, and the majority (67, 79%) had CEAP clinical class C2 venous disease. After treatment, they were monitored by clinical evaluation and Duplex imaging.

Results:
The initial treatment was completed in 93 limbs. Complications consisted of bruising (31%), tightness (17%), pain (14%), induration (2%), and superficial thrombophlebitis (2%). No severe complications were observed. Over a mean follow-up of 29 months (range 24-37), 3 patients died and 14 were lost to follow-up, leaving 88(95%) and 76(82%) limbs available for imaging surveillance at 1 and 2 years, respectively. At 3 months, treatment was anatomically successful in 84% of cases (78 complete occlusion, 7 partial occlusion, and 8 nonocclusion) and functionally successful in 89% (83 no reflux, 10 reflux). All technical failures and 73% (n=11) of the treatment failures occurred in the first half of the studied population, indicating the learning curve effect (P =.015). Mean energy delivered per unit length was 39 ± 8 J/cm (range 25-65) for successful treatment (n=78) and 30 ± 10 J/cm (range 21-50) for failed treatment (n=15). No recanalization or recurrent GSV reflux after anatomically and functionally successful treatment was observed in 73 and 61 limbs at 1- and 2-year follow-up, respectively.

Conclusion:
EVLA is a feasible, safe and fast procedure for eliminating GSV reflux and has excellent cosmetic results. Despite the learning curve, we believe that the treatment results are promising. When successful treatment is achieved by EVLA, a prospective follow-up of 2 year demonstrates durable results.

Key words:
varicose vein surgery, great saphenous vein, endovenous laser treatment.

Introduction

The standard treatment for reflux of the great saphenous vein (GSV) is ligation of the vein and its tributaries at the saphenofemoral junction (SFJ), followed by stripping of the GSV from the groin to just below the knee. The operation, which is performed under general or spinal anesthesia, is a relatively inexpensive day-care procedure that does not require specific instrumentation. Disadvantages of GSV stripping include risks associated with anesthesia, complications of saphenous nerve injury, hematoma, wound infection, and recurrence, which occurs in 20 to 80% of cases after 1 year and in 40% after 5 years[1-5].

Recently, endovenous procedures have been introduced to eliminate reflux by obliterating the GSV. Such approaches have the advantage of better cosmetic results, greater clinical improvement, fewer adverse effects, earlier return to full activity, minimal or no loss of working days, and recurrence rates not worse than those of traditional surgery. Endovenous laser treatment (EVLA) was first introduced by Boné[6]. With this procedure, the vein wall is damaged by the energy delivered from a 810-nm diode laser fiber introduced in the GSV. The primary mechanism of action of endovenous laser is transfer of laser energy from direct contact between the laser fiber and vein wall, resulting in vein wall damage, which if sufficient should lead to a fibrous strand. Duplex imaging is required to access the GSV, to confirm the position of the laser fiber at the SFJ, and to assist with infiltration of tumescent local anesthesia.

The aim of this prospective study was to evaluate the 2-year results of EVLA performed for reflux of the GSV at a single center.

Methods.

Study Design and Patient Sample

Eighty-five patients (56 women; mean age 49 years, range 27–80 years) who underwent EVLA for varicose veins due to GSV reflux during the period from January 2002 to January 2003 at our institution followed up for a minimum of 2 years. All patients were symptomatic and the majority (79%) had CEAP clinical class C2 venous disease (C2, E1, AS2, Pr in 10 and C2, E1, AS3 Pr in 57). In the other 18 patients (C3-6, E1, AS3, Pr), 10 patients had edema without skin changes, 7 patients skin changes ascribed to venous disease and 1 patient had a venous ulcer. All patients had a clinical evaluation and Duplex imaging. Duplex ultrasosongraphy was performed by a vascular laboratory technician using an ATL HDI 3500 (ATL Ultrasound, Bothell, USA) with a high-resolution 7.5 MHz linear probe, while the patient was standing, with calf manual compression-release to provoke and quantify SFJ and GSV reflux. One hundred limbs were treated; 9 limbs had previously undergone ligation of the SFJ. Anatomically, 87 limbs demonstrated reflux of the GSV, including SFJ, to below the knee (AS3), and 13 patients to above the knee (AS2). Patients with a very superficial, or tortuous GSV, and patients with a history of a deep venous thrombosis were excluded. Informed consent was obtained from all patients.

EVLA Procedure

The patients were treated on a day-care basis. According to our clinic's protocol, they all received low-molecular-weight heparin as thrombosis prophylaxis with diclofenac (100 mg) for analgesia and oxazepam (10 mg) for sedation. The patients were treated in the supine position. The exact position of the SFJ, the course of the GSV above the knee, and the access site of the GSV just below the knee were determined by ultrasound scanning. The limb was prepared with digluconate (0.5% in 70% alcohol) and draped. The ultrasound probe was placed into a sterile cover and the GSV was punctured just below the knee with a 19-gauge needle. A 0.035" J tip guide wire was introduced through the needle. After removal of the needle, a 45-cm 5 French introducer sheath was placed into the GSV over the J -tip guide wire. The internal dilator and guide wire were removed. Intraluminal position was confirmed by aspiration of blood. The tip of the sheath was positioned 1-2 cm below the SFJ under ultrasound guidance. A 600-μm core bare tip fiber, connected to the Diomed D15 surgical diode laser (Diomed Inc, Andover, MA), was inserted into the sheath and advanced until the distal marker on the fiber reached the introducer opening. While the fiber was held, the introducer sheath was withdrawn 3 cm until the proximal marker on the fiber reached the introducer opening. Under ultrasound monitoring, 200-250 mL of tumescent local anesthetic (200 mL physiological saline (0.9%), 40 mL lidocaine (1%), and adrenaline (1: 100,000) neutralized with 10 mL sodium bicarbonate (8.4%)) was administered within the facial sheath of the GSV to achieve analgesia, and compression of the vein, and a heat sink. In case of spinal anesthesia 200-250 ml NaCl % was administered. Fiber tip position was confirmed by visualization of the red aiming beam of the laser at the SF junction. Manual com-

pression was applied over the GSV while laser energy with an 810-nm wavelength was delivered endovenously at a rate of 3–4 pulses per cm (12 W, 1-s pulse, and 1-s pulse interval) from 1-2 cm below the SFJ to the access site. Additional surgical procedures were not performed at the time of the EVLA procedure. After the procedure, a graduated compression stocking, e.g. 20 -30 mm HG was worn day and night for 1 week. Pain was relieved with diclofenac (100 mg, twice daily for 1 week). Patients were instructed to walk immediately after the procedure and to resume their normal daily activities. In follow-up, patients were monitored by means of clinical evaluation and Duplex imaging, which was were performed within 6 weeks of the operation and then 3, 6, 12 and 24 months.

Definitions and Statistical Analysis

Reflux was defined as retrograde flow lasting > 0.5 seconds demonstrated with Duplex imaging. Post procedural analysis focused on reflux and occlusion of the treated vein. Non-compressibility of the treated vein segment in addition to Duplex imaging was helpful in evaluating patients post-EVLA.

Technical success was defined as procedure performed e.g. endovenous delivery of laser energy from 1-2 cm below the SFJ to the access site. Treatment success was defined as technical success, anatomical success (complete occlusion, defined as absence of flow in the treated vein segment, demonstrated with Duplex imaging), and functional success (complete freedom from reflux in the treated vein segment, demonstrated with Duplex imaging). Treatment failure was defined as technical success but neither anatomical nor functional success. Recurrent reflux and recanalization referred to events seen in Duplex imaging at any point in the treated vein after technical, anatomical, and functional success. Clinical improvement, a measure of patient satisfaction was determined with a scale: scores ranged from +3 markedly improved, + 2 moderately improved, +1 minimally improved, no change to -3 markedly worse. Clinical and duplex date were entered into Microsoft® Excel databases (Microsoft , Redmond, Washington, USA). Results were analyzed by intention to treat. Data are presented as the means ± standard deviation unless indicated elsewhere. Groups were compared using the Student t test and the Fisher exact test. $P < 0.05$ was considered to indicate a significant difference.

Results

EVLA could not be completed in 7 patients: Duplex imaging of the laser tip at the SFJ was unclear in 3 patients; the introducer sheath could not be passed upward because of a stenotic segment of the GSV above the knee due to thrombophlebitis in 1 patient; the guide wire could not be introduced in a very tortuous and enlarged GSV in 1 patient; and the GSV was perforated at the access site and the guide wire and introducer sheath were introduced into the perivenous space in 2 patients. Patients preferred general or spinal anesthesia to local anesthesia for surgery on 25 limbs. In 5 limbs the GSV was accessed above the knee and in 38 limbs venasections were required to introduce the guide wire into the GSV. Eight limbs were not free of pain during the procedure, and the laser fiber had to be pulled back faster

than normal. Post procedurally, despite anatomical and functional success, 20 limbs had persistent varicose veins of the superficial accessory of the GSV and needed additional treatment, namely, compression sclerotherapy (n =15 limbs), and Muller phlebectomy (n=5 limbs).
The post-procedural complications were bruising (31%), tightness on the medial side of the upper leg (17%), pain (14%), and palpable string/induration in the course of the GSV (2%), and superficial thrombophlebitis (2%). After 6 weeks the symptoms had diminished but were still present in 12 patients (18 limbs); they were still present in 3 patients (4 limbs) at 3 months. Tumescent local anesthesia did not cause side effects and there were no severe complications such as deep venous thrombosis and/ or pulmonary embolism (Table 1). At the 3-month follow up, Duplex imaging showed that EVLA was anatomically successful in 84% of limbs and functionally successful in 89% of limbs. Complete occlusion was demonstrated in 78 limbs, partial occlusion in 7 limbs, and nonocclusion in 8 limbs. Reflux was demonstrated in 10 limbs (nonocclusion 8, partial occlusion 2). Reflux of the SFJ, proximal GSV, and accessories of the great saphenous vein (anterior accessory of the GSV 4, posterior accessory of the GSV 2) was demonstrated in 8 nonoccluded limbs. GSV reflux without SFJ reflux was demonstrated in 2 partially occluded limbs. Of the 15 treatment failures, 8 limbs needed a second treatment, e.g. surgical stripping and the remaining 7 limbs were stable on Duplex imaging, asymptomatic, and free from varicose veins at the 1- and 2-year follow-up (Table 2).

Table 1. Postoperative complications after technically successful endovenous laser treatment of 93 great saphenous veins.

Months	0.5	1.5	3	6
None	34	75	88	93
Bruising	29	6	0	0
Tightness	16	10	3	0
Pain	13	1	0	0
Induration	2	1	1	0
Saphenous nerve damage	0	0	0	0
Skin burn	0	0	0	0
Superficial thrombophlebitis	2	0	0	0
DVT /PE	0	0	0	0

DVT/PE, deep vein thrombosis/pulmonary embolism

Table 2. Details of failures of endovenous laser treatment of 15 great saphenous veins at 3-month follow-up.

Nr	Joule	GSV(cm)	Joule/cm	occlusion	SFJ reflux	GSV reflux	Reoperation
9	1064	45	24	Partial	No	Yes	No
11	1152	41	28	Partial	No	No	No
13	731	35	21	None	Yes	Yes	Yes
20	935	41	23	None	No	Yes	Yes
22	1089	41	27	None	Yes	Yes	Yes
31	1081	42	26	None	Yes	Yes	Yes
37	1182	42	29	None	Yes	Yes	Yes
39	1212	40	30	Partial	No	No	No
42	1294	39	39	Partial	No	No	No
44	1124	45	25	None	Yes	Yes	Yes
49	1658	43	39	None	Yes	Yes	Yes
52	1860	42	42	Partial	No	Yes	No
71	1672	35	48	Partial	No	No	No
75	1724	39	44	Partial	No	No	No
88	1749	35	50	None	No	Yes	Yes

SFJ, sapheno-femoral junction; GSV, great saphenous vein.

Recanalization and recurrent GSV reflux did not occur after anatomical and functional success in 73 and 61 limbs at 1- and 2-year follow-up, respectively. After an anatomically and functionally successful procedure, the treated GSV was not identifiable with Duplex ultrasound in 89% and 90% of limbs at the 1- and 2-year follow-up, respectively. Two patients developed small saphenous vein reflux and 13 patients CEAP clinical class C1 venous disease. Information about the operating time, treated vein length, and energy delivered were available for all but 11 limbs. The mean operating time, mean treated vein length, and mean energy delivered per unit of length were 35 ± 8 min (range 21-62), 41 ± 3 cm (range 30-50), and 35 ± 8 J/cm (range 19-63), respectively. The mean energy delivered per unit of length for anatomical successful procedures (n=78) was 39 ± 8 J/cm (range 25-65) for failed procedures (n=15) 30 ± 10 J/cm (range 21-50) (Table 3).

After an anatomically and functionally successful procedure, the clinical improvement (i.e., +2 or + 3), which was used as a measure of patient satisfaction, was 98% and 92% at the 1- and 2-year follow-up assessments.

Table 3. Details of success and failures after technically successful endovenous laser treatment of 93 great saphenous veins.

	Success	Failure
Number	78	15
Length of treated GSV (cm)	42 ± 7 (range 30-50)	42 ± 5 (range 35-47
Energy delivered (J)	1623 ± 312 (range 972-2665)	1194 ± 345 (range 731-1749
Energy delivered per unit of length (J/cm)	39 ± 8 (range 24-65)	30 ± 10 (range 21-50)

Discussion

The reason for using a diode laser as a replacement for surgical procedures is based on the unique characteristics of laser light. The fundamentals have been previously prescribed[8]. In this study our initial experience and 2 year results of a single centre with endovenous laser treatment for reflux of the great saphenous vein are presented. We experienced a learning effect in the use of EVLA for reflux of the GSV (Fig 1). Initially, we had a 7% technical failure rate, difficulty gaining access to the GSV with Duplex imaging, a mismatch of the sheath length and the length of the treated GSV, and problems with inadequate delivery of anesthesia into the facial sheath of the GSV, such that patients experienced pain during injection and in particular with laser coagulation. All technical failures (n=7) occurred in the first half of the studied population. This learning effect with regard to Duplex-guided access to the GSV has meant that the number of venasections had decreased significantly from 29 (58%) in the first 50 procedures to 9 (18%) in the last 50 procedures. There was also a learning effect regarding the treatment result itself: 73% (n=11) of the treatment failures occurred in the first half of the studied population. In these failures the sheath was too short in 3 limbs; 8 patients, treated with tumescent local anesthetic, were not free of pain during the procedure and in spite of more tumescent anesthetic volume the laser fiber had to be pulled back faster than normal, and the dose of laser power was also lower than normal. We reduced the inconvenience of injections and pain during the procedure by using a larger volume of the tumescent local anesthetic and added sodium bicarbonate. In cases of mismatch between catheter and vein we positioned the tip of the laser fiber itself in the right position.

We have determined that not all patients are candidates for this procedure. For example, patients with an inappropriate diameter of the GSV (< 0.4 cm) or a history of superficial thrombophlebitis involving the GSV resulting in blockage are not suitable for EVLA because their veins would not allow endovenous introduction and passage of the catheter.

Patients experience minimal discomfort after the procedure, with slight bruising and tightness on the medial side of the leg in the first days after the procedure. Bruising (31%) is seen in the first week after the operation but is less than that usually seen

after surgical stripping. Delivery of tumescent anesthesia contributes to bruising, however the extent and severity of bruising does not correlate to post-EVLA discomfort. Contact between the laser fiber and vein wall is necessary, to allows adequate transfer of laser energy to the target vein wall, resulting in vein wall damage and subsequent fibrosis. Inadequate vein emptying with too much blood remaining within the vein will lead to non-target heating. In the latter case if occlusion occurs, it will be the result of thrombosis with inevitable vessel recanalization. Tightness (17%) of the treated vein does not correspond to presence or degree of bruising and is most likely caused by acute inflammation with transverse and longitudinal retraction of the vein.

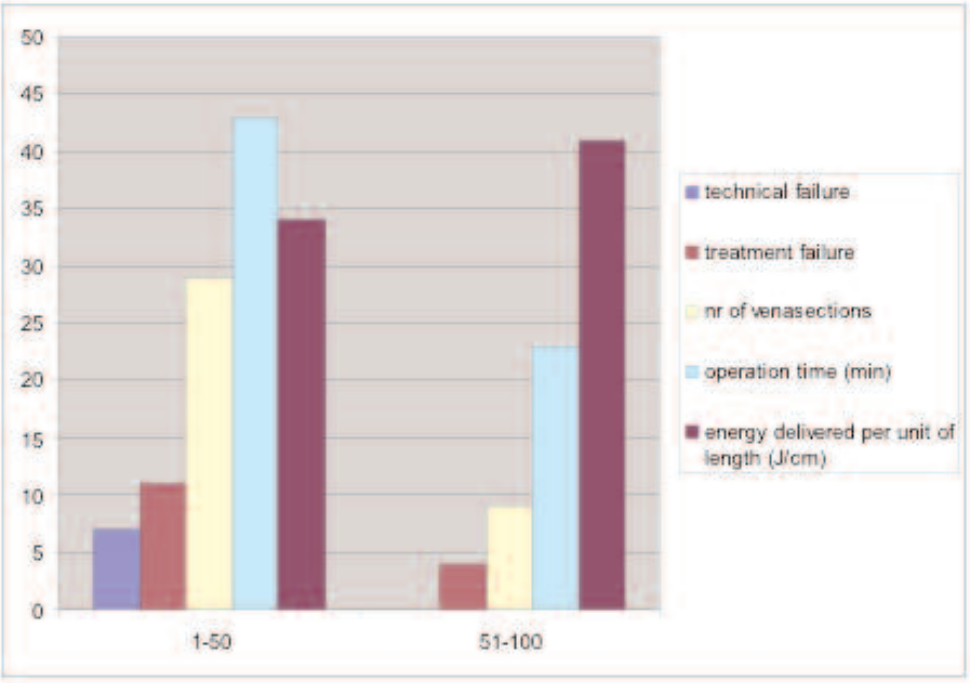

Fig 1. Details of the first 50 endovenous laser procedures compared with the second 50 procedures, indicating the learning curve effect.

Our results, with 93% technical success, 84% anatomical success, and 89% functional success at 2 years, are comparable with those of other studies (Table 4). However, only a few studies have reported on their late results, especially late recanalization. Standardization of energy delivered per unit of length and pullback rate is necessary for interpretation of the clinical results. The success or failure of EVLA seems to be associated with the dose of energy delivered[17,18] (Table 5). After evaluation of our first 100 procedures and in accordance with Min et al[10], we have increa-

sed the dose by raising the laser output from 12 to14 watt, switched from pulsed mode to continuous mode, and lowered the pullback rate to 0.3-0.4 cm /s. We now deliver more energy in the proximal part of the GSV than in the distal part. It is assumed that continuous delivery of laser energy in combination with a slow pull-back rate will improve the occlusion rate[10, 14]. There is no significant difference in steam bubble generation and success rates between 810 nm, 940 nm, and 980 nm diode lasers[15].

In an effort to prevent vessel wall perforation, and hence post-procedural bruising, Goldman[16] found a 1320-nm continuous laser with automatic catheter withdrawal to be better suited for GSV obliteration than other laser wavelengths. However, more needs to be known about the mode of action of laser and the technique

Table 4. Anatomical success rates reported for endovenous laser treatment of the great saphenous vein.

Author, year	No limbs	Wave Length of laser	Follow-up period	Overall success	Not occluded or recanalized at 3 mo	Not occluded or recanalized at 12 mo	Not occluded or recanalized at 24 mo
Navarro, 2001	40	810	14	100%	0%		
Min, 2001	90	810	9	96%	4%		
Gerard, 2002	20	980	1	90%	-		
Proebstle, 2002	31	940	1	97%	-		
Min, 2003	499	810	39	93,4%	1.8%	2.2%	6.6%
Proebstle, 2003	109	940	12	90,4%	4.8%	4.8%	-
Oh, 2003	15	980	3	100%	-		
Perkowski, 2004	203	940	12	97%	3%	0%	-
Proebstle, 2004	106	940	3	90%	10%	-	
Navarro, 2004	200	810	48	97%	not reported	not reported	3% at 48 mo
Timperman, 2004	111	810-940	18	77,5%	not reported	not reported	
Goldman, 2004	24	1320	6	100%	0%	-	
Disselhoff, 2005	100	810	36	84%	16%	0%	0%

needs to be optimized before results will improve. Proebstle et al[14,15], considered the vessel wall to be damaged mainly as a result of steam bubble-mediated thermal damage, with subsequent thrombotic occlusion. Min et al[10] stated that EVLA closure results from heat-induced shrinkage of the vein wall. Since blood is a chromophore for all laser wavelengths used for endovenous ablation, too much blood will

lead to inadequate vein wall damage. Occlusion by thrombosis will result in eventual recanalization and treatment failure. Steam bubble formation will not cause sufficient vein wall injury, rather the goal is to maximize laser energy transfer to the vein wall by ensuring contact between the vein wall and laser tip. Manual compression in combination with appropriate administration of tumescent local anesthetic is one means to accomplish this. Combined with delivery of an adequate dose of laser energy, the result should be non-thrombotic occlusion of the vein. Recently, we presented some preliminary data on thermal imaging techniques and intravascular temperature measurement of EVLA in an experimental setting. We suggested that a clot forms at the tip of the laser fiber, which effectively creates vapor bubbles that occupy a large volume of the vein and expose the wall to temperatures of about 100 ^{0}C. The temperature inside the vein remains high for a long time after exposure but does not extend outside the vessel[19].

In summary, we conclude that EVLA is a feasible, safe, and fast procedure for eliminating GSV reflux and has excellent cosmetic results. We believe that, despite there being a learning curve, the treatment results are promising. More knowledge of the mode of action is required for optimization of the technique and to increase the anatomical and functional success rate. After successful treatment, there is a very low rate of recanalization of the GSV, which suggests that the procedure provides long-lasting results.

Table 5. Laser energy delivered per unit of length reported in different studies of endovenous laser treatment of the great saphenous vein .

Author, year	Success		Failure	
	No of limbs	Mean energy delivered (J/cm)	No of limbs	Mean energy delivered
Proebstle,2004	96	23.8 (20.1-27.2)*	11	19.3 (15.9-23.5)*
Timperman,2004	85	63,4 ± 26.6 (20.5-137.8)	26	46.6 ± 13.8 (25.7-78
Disselhoff,2005	78	39 ± 8 (25-65)	15	30 ± 10(21-50)

References

1. Sarin S, Scurr JH, Coleridge Smith PD. Assessment of stripping the long saphenous vein in the treatment of primary varicose veins. Br J Surg. 1992;79: 889-883.
2. Dwerryhouse S, Davies B, Harradine K, Earnshaw JJ. Stripping of the long saphenous vein reduces the rate of re-operation for recurrent varicose veins: five year results of a randomized trial. J Vas Surg. 1999;29(4):589-592.
3. Van Rij AM, Jiang P, Solomon C, Christie RA, Hill GB. Recurrence after varicose vein surgery: a prospective long-term clinical study with duplex ultrasound scanning and air phlethysmography. J Vasc Surg. 2003;38:935-943.
4. Campbell WB, Vijay Kumar A, Collin TW, Allington JL, Michaels JA. The outcome of varicose vein surgery at 10 years: clinical findings, symptoms and patient satisfaction. Ann R Coll Surg Engl. 2003; 85:52-57.
5. Wintertborn RJ, Foy C, Earnshaw JL. Causes of varicose vein recurrence: Late results of a randomized trial of stripping of the long saphenous vein. J Vasc Surg. 2004;40:634-639.
6. Boné C. Tratamiento endoluminal de las varices con laser de diode studio preliminary. Rev Patol Vasc. 1999;5:35-46.
7. Porter JM, Moneta GL. Reporting standards in venous disease: an update. International consensus committee on chronic venous disease. J Vasc Surg. 1999;21:635-645.
8. Verdaasdonk RM. Medical Lasers: fundamentals and applications. Medical Lasers. 181-225.
9. Navarro L , Boné C. Endolaser: four years of follow-up evaluation. 2003 UIP World congress(abstract).
10. Min RJ, Khilnani N, Zimmet SE. Endovenous laser treatment of saphenous vein reflux: long term results. J Vasc Interv Radiol 2003; 14:991-996.
11. Proebste TM, Gül D, Lehr HA, Kargl A, Knop J. Infrequent early recanalization of greater saphenous vein after endovenous laser treatment. J Vasc Surg 2003;38:511-516.
12. Oh CK, Jung DS, Jang HS, Kwon KS. Endovenous laser surgery of the incompetent greater saphenous vein with a 980 nm diode laser. Dermatol Surg 2003; 29:1135-1140.
13. Perkowski P, Ravi R, Gowda RCN, Olsen D, Ramaiah V, Rodriguez-Lopez JA et al. Endovenous laser ablation of the saphenous vein for treatment of venous insufficiency and varicose veins: early results from a large single center experience. J Endovasc Ther. 2004Apr; 11(2):132-138.
14. Proebstle TM, Lehr HA, Kargl A, EspinolaKlein C, Rother W, Berthge S et al. Endovenous treatment of the greater saphenous vein with a 940-nm diode laser: thrombotic occlusion after endoluminal thermal damage by laser generated steam bubbles J Vasc Surg. 2002; 35(4): 729-736.
15. Proebstle TM, Sandhofer M, Kargl A, Gul D, Rother W, Knop J et al. Thermal damage of the inner vein wall during endovenous laser treatment: key role of energy absorption by intravascular blood. Dermatol Surg. 2002; 28(7): 596-600.

16. Goldman MP, Maurico M, Rao J. Intravascular 1320 nm laser closure of the great saphenous vein: a 6-12 month follow-up study. Dermatol Surg. 2004; 30(11):1380-1385.
17. Proebstle TM, Krummenauer F, Gul D, Knop J. Nonocclusion and early reopening of the great saphenous vein after endovenous laser treatment is fluence dependent. Dermatol Surg 2004; 30(2): 174-178.
18. Timperman PE, Sichlau M, and Ryu RK. Greater energy delivery improves treatment success of endovenous laser treatment of incompetent saphenous veins. J Vasc Interv Radiol. 2004;15:1061-1063.
19. Verdaasdonk RM, Disselhoff BCVM, Berg van N, Kinderen der DJ. Mechanism of endovenous laser treatment revealed using close up and thermal visualization techniques. 2005 SPIE Congress (abstract 5686-7).

Chapter 4

Randomized clinical trial comparing endovenous laser ablation of the great saphenous vein with and without ligation of the saphenofemoral junction: 2-year results

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Objective:
To evaluate whether ligation of the saphenofemoral junction (SFJ) improves the 2-year results of endovenous laser ablation (EVLA).

Methods:
Forty-three symptomatic patients with bilateral varicose veins were studied in which one limb was randomly assigned to receive EVLA without SFJ ligation, whereas the other limb received EVLA with SFJ ligation. Duplex-based groin varicose vein recurrence, abolition of great saphenous vein (GSV) reflux, and venous clinical severity score (VCSS) were investigated at 6, 12, and 24 months after treatment.

Results:
Two-year life table analysis showed freedom from groin varicose vein recurrence in 83.3% of limbs (95% CI; 67.2–94.7) in the EVLA without ligation group and in 87.4% (95%; CI 72.6–96.7) of limbs in the EVLA with ligation group (P=0.4654). Thirty-eight (88.4%) treated GSV segments were ablated completely in the EVLA without ligation group and 42 (97.7%) in the EVLA with ligation group (P=0.2020). Groin recurrence was due to an incompetent SFJ/GSV (9.3%) and to incompetent tributaries (7.0%) in the EVLA without ligation group and due to neovascularization (11.6%) in the EVLA with ligation group. The VCSS improved significantly and was comparable in both groups.

Conclusion:
There is no difference in SFJ ligation to EVLA in the short-term outcome. Whether SFJ ligation results in a poorer long-term outcome because of neovascularization has to be studied in larger populations with longer follow-up. Registration number: ISRCTN60300873 (http://www.controlled-trials.com).

Key words:
endovenous laser ablation, saphenofemoral ligation, and recurrent varicose veins.

Introduction

Endovenous laser ablation (EVLA) is used to treat varicose veins due to reflux in the great saphenous vein (GSV). It causes thermal damage to the wall of the vein, resulting in destruction of the endothelium of the intima and in denaturation of the collagen in the media, accompanied by fibrotic occlusion of the vein[1]. Critics of endovenous techniques in the treatment of varicose veins dispute the wisdom of not ligating the proximal GSV and groin tributaries at the saphenofemoral junction (SFJ), arguing that groin tributaries may remain patent, which might promote recurrence of varicose veins. Others argue that avoiding surgical disruption of the SFJ, as occurs during ligation, may actually reduce neovascularization, leading to a reduced rate of recurrence[2]. Other suggested reasons for vein ligation are failure of vein occlusion based on a "too large" diameter of the saphenous vein, and the development of a deep vein thrombosis or a pulmonary embolus[3].

The aim of this single-centre randomized clinical trial was to evaluate the 2-year results of EVLA of the great saphenous vein with and without SFJ ligation in patients with primary bilateral varicose veins.

Patients and Methods

Consecutive patients with primary bilateral varicose veins, referred to our hospital from March 2003 to February 2005, were considered for inclusion in this study. The study protocol was approved by the regional ethics committee of the Mesos Medical Centre, Utrecht, The Netherlands.

The inclusion criteria were patients with primary symptomatic varicose veins, CEAP clinical class C2 venous disease[4], age 20–75 years, SFJ incompetence, and GSV reflux from the groin to below the knee, defined as retrograde flow lasting longer than 0.5 seconds on Duplex scanning (ATL 3500 HDI, ATL ultrasound, Bothell, WA, USA). Incompetence in perforator veins, tributaries at the SFJ and accessory saphenous veins was defined as bidirectional flow. Reasons for exclusion were previous venous surgery a history of suspected or manifest deep venous thrombosis CEAP clinical class C3-6 venous disease, deep venous reflux , incompetence of the perforating veins below the knee , reflux of the GSV just to the knee , duplication of the GSV, patient refusal and others . All patients fulfilling the inclusion criteria received written and verbal information about the aims and content of the study in accordance with the Helsinki Declaration. After they had given written informed consent, patients were randomly assigned using numbered and sealed envelopes containing data concerning the side of SFJ ligation Patients received bilateral treatment in which one limb received EVLA without SFJ ligation, whereas the other limb received EVLA with SFJ ligation. The procedures were performed as day-care procedures within 6 weeks of randomization. One surgeon experienced in EVLA techniques and varicose vein surgery performed all the procedures. According to our clinic's protocol, all patients received low-molecular-weight heparin as thrombosis prophylaxis. A standard set of information was collected at each visit. Physicians used the venous clinical severity score (VCSS) [5] to assess patient's signs and symptoms and completed the CEAP classification.. For operative time we measured the duration of treatment per limb: time of laser procedure versus time of laser procedure and time of SFJ ligation (skin to skin).Postoperatively, information was collected about complications, wound closure (using the modified Hollander cosmetics score, MHCS[6]), the mean pain score and the mean reduction in physical activity score (both assessed with a linear analogue scale for grading severity on a score from 0 to 10), the mean duration of sick leave, recurrent varicose veins demonstrated at Duplex ultrasound, and scores for VCCS. Duplex-based recurrent varicose veins were classified in accordance with Stonebridge.[7] Abolition of GSV reflux was demonstrated by its complete occlusion or obliteration, confirmed by Duplex ultrasound. Special attention was paid to visualization of the GSV after EVLA to detect recanalization of this vein. There were differences in the delivery of laser energy. EVLA was performed with an 810-nm diode laser (Diomed Inc, Andover, MA) using 12-Watt intermittent laser power (1 second on, 1 second off) in the first 40 limbs (46.5%) in 20 patients, and using 14-Watt continuous laser power (at a pullback rate of 0.2 cm/s) in the next 46 limbs (53.5%) in 23 patients. The change in delivery of laser energy from intermittent to continuous was based on our first 100 procedures[8] and in accordance with Min et al[9]. It was assumed that a higher dose of laser energy (as per continuous

laser protocol) in combination with a slow pull-back rate would improve the occlusion rate[9,10].
The EVLA procedure has been described before[8]. In brief, the GSV, 5 cm below the knee, was accessed under ultrasound guidance and the tip of the laser fibre was positioned 0.5–1cm below the SFJ. Under ultrasound monitoring, 250 mL of tumescent local anaesthetic (200 mL physiological saline (0.9%), 40 mL lidocaine (1%), and adrenaline (1: 100,000) neutralized with 10 mL sodium bicarbonate (8.4%)) was administered within the facial sheath of the GSV to achieve analgesia, compression of the vein, and a heat sink. In the case of spinal or general anaesthesia, 250 ml NaCl 0.9% was administered. Manual compression was applied over the GSV while 12-Watt intermittent (1 pulse on, 1pulse off) or 14-Watt continuous laser energy was delivered from 0.5–1 cm below the SFJ to the access site at a pullback rate of 0.2 cm/s. High ligation was performed through a 4-cm-long incision in the groin, with flush division of the GSV and division of all tributaries behind the second level of division. The groin incision was closed with tissue adhesive Dermabond® (Johnson & Johnson, NJ, USA). After the procedure, a graduated long compression stocking (20–30 mmHg) was worn day and night for 1 week. Aceclofenac 100 mg twice daily for 1 week was prescribed for postoperative pain. Patients were instructed to walk immediately after the procedure and were encouraged to resume normal activities and work as soon as possible. The primary outcome measure was freedom from recurrent varicose veins in the groin, as confirmed by Duplex ultrasound, 2 years after treatment. Secondary outcomes were abolition of reflux in the GSV, scores for VCSS, freedom from overall recurrent varicose veins, and procedural complications, Follow-up at 6, 12, and 24 months was complete for 86 limbs (100%), 82 limbs (95.3%), and 78 limbs (90.6%), respectively. Two patients were lost to follow-up at 12 months because of discomfort during Duplex examination and 2 at 24 months because of pregnancy. Earlier ultrasound scanning did not detect evidence of groin recurrence and revealed abolition of GSV reflux in these 4 patients; their VCSS scores had also improved.

Statistical analysis
We hypothesized that high ligation would not improve the outcome of EVLA 2 years after treatment. To our knowledge in 2003, there were no randomized controlled trial data available comparing different options for venous surgery in the same patient with primary varicose veins. So, a formal power calculation was not performed. The precision of a trial with 43 as the denominator will yield a standard error of 5.7% (pertaining to a proportion of 85%). Analysis of outcome was on an intention- to-treat basis. Data from the assessments were coded and analyses were performed using SAS® 8.2 statistical programs (SAS Institute, North Carolina, USA) and Microsoft® Excel (Microsoft Redmond, Washington, USA). The unit of the primary analyses was limb, taking into account the paired nature of the study design. The difference in primary outcome for EVLA without ligation versus EVLA with ligation was assessed by means of the McNemar's test, a matched pairs test for a 2x2 table. Freedom from Duplex-based recurrence was graphically depicted by means of Kaplan-Meier cur-

ves, assuming the event took place exactly half way two follow-up visits and difference assessed by means of the log-rank test. All secondary analyses on count variables were tested with the McNemar's test and continuous variables with paired t-test. Multivariate repeated measures general linear modelling was used to compare scores for VCSS over time. $P < 0.05$ was considered to indicate a statistical significant difference.

Results

Of 145 patients assessed for the trial, 49 (33.8%) met the inclusion criteria and 43 (29.7%) agreed to randomization (Fig.1). The median age of the patients was 45 years (range 23-74). Thirty-six patients (83.7%) were female and 27 (62.8%) had a body mass index less than 25 kg/m2. Baseline characteristics of the GSV are given in Table 1. The mean operative time, was significantly longer in the EVLA with ligation group than in the EVLA group (32.4 ± 5.8 min versus 19.8 ± 6.3 min; $P<0.0001$). The mean length of treated vein was statistically significantly greater (42.9 ± 2.8 cm versus 41.4 ± 3.1cm; $P<0.0001$) in the EVLA group but this was not of clinical consequence. Reflux in the small saphenous vein (SSV) was treated with saphenopopliteal ligation in 4 of the 86 limbs affected (4.7%); 2 in each group. At 6 weeks, residual non-GSV varicose veins in 18 limbs underwent sclerotherapy with aethoxysclerol 1%, with the intention of removing all varicosities. The mean reduction in physical activity score during the first 10 days after treatment was 2.1 (range 0–8) and the mean duration of sick leave was 0.6 days (range 0–6).

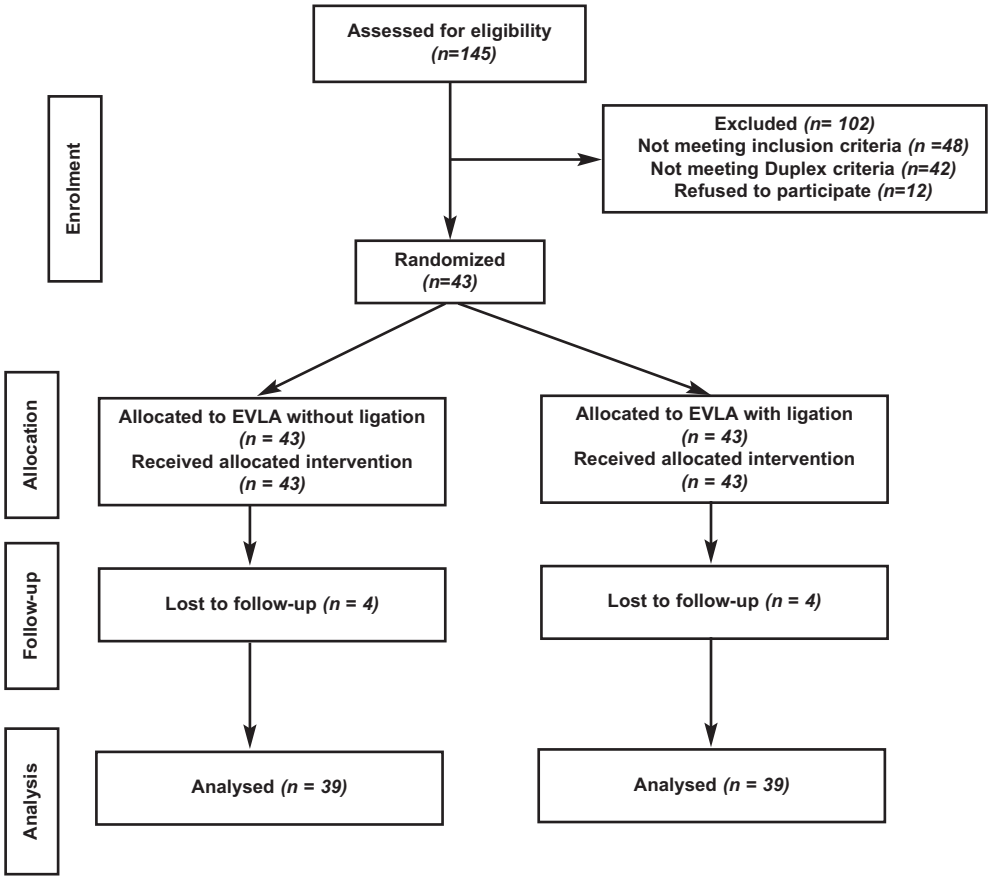

Fig. 1 CONSORT flow chart. EVLA, endovenous laser ablation.

Table 1 Recurrent varicose veins demonstrated at Duplex ultrasound and scores for VCCS.

	baseline	**6 month** (n= 43)	**1 year** (n=41)	**2 year** (n=39)
Type 1a recurrence				
EVLA without ligation		4	0	0
EVLA with ligation		0	0	0
Type 1b recurrence				
EVLA without ligation		0	3	0
EVLA with ligation		0	0	0
Type 1c recurrence				
EVLA without ligation		0	0	0
EVLA with ligation		0	2	3
Type 2a recurrence				
EVLA without ligation		0	0	0
EVLA with ligation		0	0	0
Type 2b recurrence				
EVLA without ligation		0	0	3
EVLA with ligation		1	1	3
Saphenous vein recurrence				
EVLA without ligation		0	1	1
EVLA with ligation		0	0	1
No recurrence				
EVLA without ligation		39	35	31
EVLA with ligation		42	39	32
VCSS sore*				
EVLA without ligation	3.1 (1-5)	1.0 (0-4)	0.5 (0-2)	0.5 (0-2)
EVLA with ligation	3.1 (1-5)	0.9 (0-3)	0.5 (0-2)	0.5 (0-2)

*Type 1a: incompetent great saphenous vein (GSV). Type 1b: incompetent tributaries. Type 1c: neovascularization (defined as serpentine tributaries arising from the ligated SFJ. Type 2a: cross-groin connections. Type 2 b: thigh perforators. EVLA, endovenous laser ablation. VCSS, venous clinical severity score. *Values are mean (range).*

Primary outcome

Two-year life table analysis (Figure 2) showed freedom from varicose vein recurrence in the groin in 83.3% of limbs (95% CI; 67.2–94.7) in the EVLA group and in 87.4% of limbs (95%; CI 72.6–96.7) in the EVLA with ligation group (P=0.4654). In the EVLA without ligation group, 4 limbs (9.3%) had type 1a varicose vein recurrence and no improvement in VCSS scores requiring additional SFJ ligation at the 6-month follow-up. Three 3 (7.0%) limbs had type 1B varicose veins recurrence (anterior saphenous vein n = 3) at the 12-month follow-up in which no improvement in VCSS scores was recorded in 2 limbs and required additional sclerotherapy. In the EVLA with ligation group, 5 limbs (11.6%) had type 1C varicose veins recurrence in which no improvement in VCSS scores was recorded in 3 limbs; sclerotherapy was performed in 2 limbs (Table 1).

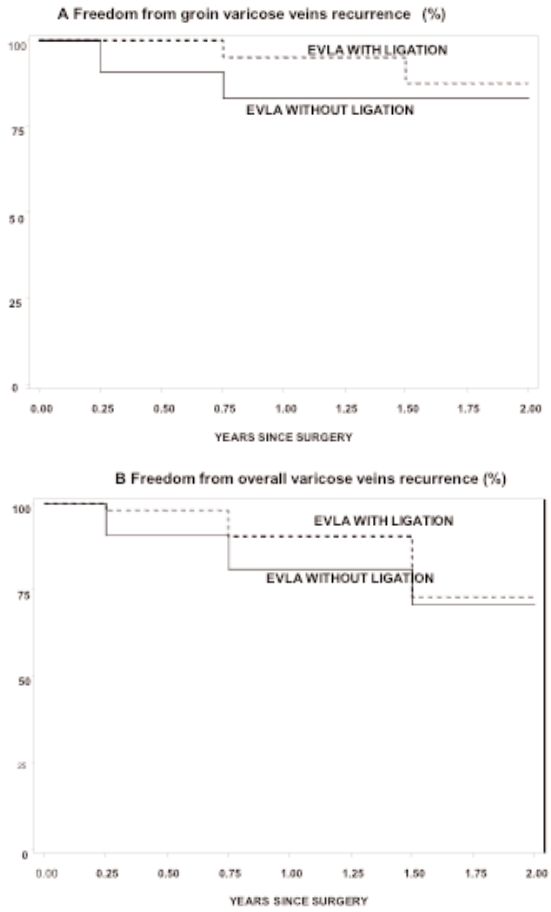

Fig. 2 Kaplan–Meier life table analysis of freedom of A groin varicose vein recurrence and B overall varicose vein recurrence.

Secondary outcomes

In the EVLA without ligation group 38 (88.4%) treated GSV segments were ablated completely (continuous exposure n= 22, 95.0%, intermittent n=16, 80%) and in the EVLA with ligation group 42 (97.7%) treated GSV segments (continuous n=23,100%, intermittent n=22, 95.6%. (P=0.2020). Although continuous exposure resulted in abolition of GSV reflux in more limbs than did intermittent exposure (97.8% (45/46) versus 87.5% (35/40), P=0.2188, respectively), the differences between the two groups not significant. At the 12- and 24-month follow-ups, recanalization of the GSV was not observed in either group. Scores for VCSS improved significantly in both groups, but the differences between the groups were not significant and were independent of time since the procedure (Table 2).

Two-year life table analysis showed freedom from overall varicose vein recurrence in 70.8% of limbs (95% CI; 51.3–86.5) in the EVLA group and in 72.8% of limbs (95% CI; 52.8–87.3) in the EVLA with ligation group (P=0.6718), respectively (Figure 2). There were no significant differences between the groups concerning bruising (53.5% in the EVLA group and 58.1% in the EVLA with ligation group, P=0.4142), pain score (3.6±2.1 and 3.6±2.4, P=0.9743), tightness along the course of the GSV (83.7% and 79.1%, P= 0.4142), and superficial thrombophlebitis (6.9% and 2.3%, P=0.3173). No patients had skin burns and there were no major complications such as deep vein thrombosis and /or pulmonary embolism. Wound complications occurred in four limbs in the EVLA with ligation group (haematoma, n=2; dehiscence, n=1; superficial groin infection, n=1) but in none in the EVLA group. None of the wound complications required surgical treatment. The proportion of patients in the EVLA with ligation group with an optimal wound EVLAluation score (MHCS = 6) was 74.4% (32/43) at 10 days and 95.3% (41/43) at 6 weeks after treatment.

Table 2 Preoperative Duplex results

	EVLA without ligation (n = 43)	EVLA with ligation (n = 43)	P value
In GSV at SFJ*			
Diameter (cm)	0.9 (0.4-1.7)	0.9 (0.5-1.6)	0.9564
Reflux time (s)	3.4 (0.5-6.0)	3.3 (0.5-6.4)	0.4380
In GSV mid thigh*			
Diameter (cm)	0.7 (0.4-1.6)	0.6 (0.3-1.6)	0.4336
Reflux time (s)	3.7 (0.5-6.0)	3.6 (0.5-6.0)	0.7690
In GSV at knee*			
Diameter (cm)	0.6 (0.4-1.6)	0.6 (0.3-1.6)	0.2856
Reflux time (s)	4.0 (0.5-6.0)	3.9 (0.5-6.0)	0.6896
In GSV mid calf*			
Diameter (cm)	0.4 (0.2-0.8)	0.4 (0.2-0.6)	0.9099
Reflux time (s)	1.2 (0.0-6.0)	1.2 (0.0-6.0)	0.7781
External pudendal vein			
Reflux	0	1	0.7092
No reflux	28	27	
Not visible	15	15	
Superficial epigastric vein			
Reflux	2	1	0.9241
No reflux	28	28	
Not visible	13	14	
Superficial circumflex iliac vein			
Reflux	0	2	0.1819
No reflux	23	25	
Not visible	20	16	
Anterior saphenous vein			
Reflux	3	6	0.3430
No reflux	32	30	
Not visible	8	7	
Posterior saphenous vein			
Reflux	5	4	0.9115
No reflux	28	30	
Not visible	10	9	
Superficial saphenous vein			
Reflux	0	0	0.4142
No reflux	35	33	
Not visible	8	10	

** values are mean (range). GSV, great saphenous vein; SFJ saphenofemoral junction*

Discussion

In this single-centre intra-patient study, we found no difference in short-term outcome between EVLA alone and EVLA with SFJ ligation. A tendency was observed that SFJ ligation, resulted in a poorer long-tem outcome due to neovascularization The VCSS improved significantly and was comparable in both groups. EVLA proved to be very effective in causing ablation of the GSV with a maximal diameter of 17 mm: there was a flush occlusion with the femoral vein in 43 (100%) limbs in the EVLA with ligation group and occlusion from 1cm below the SFJ was demonstrated in 40 (93.1) limbs in the EVLA without ligation group. Two earlier reports of EVLA with SFJ ligation reported comparable results: Chang et al[11] reported a success rate of 96.8% in 244 limbs followed up to 28 months, and Huang et al[12] reported 100% GSV occlusion in 94 limbs with a median follow-up of 6 months. A systematic review of EVLA alone by Mundy et al[13] reported a GSV occlusion rate of 87.9–100%. In our study, we found that recurrent varicose veins in the groin were due to an incompetent SFJ/GSV in four limbs (9.3%) in the EVLA group but in none (0%) of the EVLA with ligation group. Non-proximal GSV occlusion and/or early recanalization are reported in fewer than 10% of veins after EVLA[14]. Proebstle et al[15] suggested that pretreatment diameter does not influence the success of EVLA although the laser energy delivered might need to be adjusted. We found that continuous exposure was more effective than intermittent exposure in abolishing GSV reflux (in 97.8% versus 87.5% limbs, respectively; P=0.2188). As stated by other authors [16-19] successful GSV ablation depends on the mode and amount of laser energy delivered, laser wavelength, and pullback rate, but also on methodological aspects, such as the use of perivenous infiltration, manual compression over the vein during the procedure, and a fibre tip position 0.5–1 cm below the SFJ. These aspects are not discussed in this article.

Groin recurrence due to incompetent anterior accessory saphenous occurred in three limbs (7%) after EVLA alone but in none (0%) after EVLA with ligation. Reflux in SFJ tributaries such as the anterior accessory saphenous vein is an important cause of recurrence. Garner[20] reported that of 141 groin recurrences after surgical stripping, 61 (43%) were due to a persistent anterior accessory saphenous vein. In our study, we found that of 206 (79.8%) visible SFJ tributaries at preoperative Duplex scanning, 18 (8.7%) had reflux in one or more SFJ tributaries; these were treated with sclerotherapy 6 weeks after EVLA. Non-refluxing GSV tributaries were found in 198 limbs (76.7%) at Duplex scanning, of which only 3 (1.5%) resulted in recurrence. In accordance with Theivacumar[18], we believe that non-refluxing GSV tributaries should not be treated at initial therapy because they do not have an adverse effect on outcome 2 years after EVLA.

We observed groin vein recurrence due to neovascularization in five limbs (11.6%) after EVLA with ligation and in none (0%) after EVLA alone. In their prospective study comparing radiofrequency ablation (VNUS Closure) and surgical stripping, Kianifard et al[19] did not observe neovascularization at the SFJ in any of the patients who had undergone radiofrequency ablation but did in 11% of patients who underwent surgical stripping. According to van Rij et al[22], the rate of groin varicose vein

recurrence after adequate surgery is 23%, of which neovascularization accounts for 85%. The notion that neovascularization in the groin after surgical treatment leads to recurrence is supported by histological evidence. Glass[21] described healing angiogenesis induced by the groin wound as a major source of new channels reconnecting superficial veins to the deep femoral vein around a ligated SFJ. Thus, interference with the venous drainage of the lower abdominal and pudendal veins may promote new vessel formation. The absence of neovascularization in the EVLA without ligation group may be explained by the closed technique that does not result in groin haematoma and angiogenesis.
In conclusion, we found no difference in short-term outcome between EVLA and EVLA with SFJ ligation. Whether SFJ ligation results in a poorer long-term outcome because of neovascularization has to be studied in larger populations with longer follow-up.

Limitations
The participants and the observers in the study were obviously aware of which intervention was performed due to scarring in the groin (lack of blinding).

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References
1. Disselhoff BC, Rem AI, Verdaasdonk RM, der Kinderen DJ, and Moll FL. Endovenous laser ablation: an experimental study on the mechanism of action. Phlebology:2008;2:69-76.
2. Chandler JG, Pichot O, Sessa C et al. Defining the role of extended saphenofemoral junction ligation: a prospective comparative study. J Vasc Surg 2000; 32:941-953.
3. Mozes G, Kalra M, Carmo M, Swenson L et al. Extension of saphenous thrombus into the femoral vein: A potential complication of new endovenous techniques. J Vasc Surg 2005; 41:130-135.
4. Porter JM, Moneta GL. Reporting standards in venous disease: an update. International consensus committee on chronic venous disease. J Vasc Surg 1999;21:635-645.
5. Rutherford RB, Padberg FT jr, Comerota AJ, Kistner RL et al. Venous severity scoring: an adjunct to venous outcome assessment. J Vasc Surg 2000; 1:1307-1312.
6. Hollander JE, Singer AJ, valentine S, Henry MC. Wound registry: Development and validation. Ann Emerg Med 1995; 25(5): 675-685.
7. Stonebridge PA, Chalmers N, Beggs I, Bradburry AW et al. Recurrent varicose veins: a varicographic analysis leading to a new practical classification. Br J Surg 1995; 82 (1); 60-62.

8. Disselhoff BC, der Kinderen DJ. Moll FL. Is there recanalization of the great saphenous vein 2 years after endovenous laser treatment? J Endovasc Ther 2005; 12:731-738.
9. Min RJ, Khilnani N, Zimmet SE. Endovenous laser treatment of saphenous vein reflux: long term results. J Vasc Interv Radiol 2003; 14:991-996.
10. Timperman PE, Sichlau M, and Ryu RK. Greater energy delivery improves treatment success of endovenous laser treatment of incompetent saphenous veins. J Vasc Interv Radiol. 2004;15:1061-1063.
11. Chang CJ and Chua J. Endovenous laser photocoagulation for varicose veins. Laser Surg Med 2002; 31: 257-262.
12. Huang Y, Jiang M, Li W, Lu X et al. Endovenous laser treatment combined with a surgical strategy for treatment of venous insufficiency in lower extremity: A report of 208 cases. J Vasc Surg 2005; 42:494-501.
13. Mundy L, Merlin TL, Fitridge RA and Hiller JE. Systematic review of endovenous laser treatment for varicose veins. Br J Surg 2005; 92:1189-1194.
14. Proebstle TM, Gül D, Lehr HA, Kargl A, Knop J. Infrequent early recanalization of greater saphenous vein after endovenous laser treatment. J Vasc Surg 2003; 38:511-516.
15. Proebstle TM. Krummerauer F, Gul D, Knop J. Non-occlusion and early reopening of the great saphenous vein after endovenous laser treatment is fluence dependent. Dermatol Surg 2004;30:174-178.
16. Proebstle TM, Moehler T, Herdemann S. Reduced recanalization rates of the great saphenous vein after endovenous laser treatment with increased energy dosing; definition of a threshold for the endovenous fluence equipment. J Vasc Surg 2006; 44:834-839.
17. Ravi R, Rodriquez-Lopez JA, Trayler EA, Barrett DA et al. Endovenous ablation of incompetent saphenous vein: a large single-centre experience. J Endovasc Ther 2006; 13: 244-248.
18. Theivacumar NS, Dellagrammaticas D, Beale RJ, Mavor AI et al. Fate and clinical significance of saphenofemoral junction tributaries following endovenous laser ablation of great saphenous vein. Br J Surg 2007;94:722-725.
19. Kianifard B, Holdstok JM, Whiteley MS. Radiofrequency ablation (VNUS closure) does not cause neo-vascularisation at the groin at one year: results of a case controlled study. Surgeon 2006:4(2):71-74.
20. Garner JJ, Heppelt PS and Leopold PW. The lateral accessory saphenous vein-a common cause of recurrent varicose veins. Ann R Coll Surg Engl 2003; 85:389-392.
21. Glass GM. Neovascularization in recurrence of the varicose great saphenous vein following transaction. Phlebology 1987;2:81-91.
22. van Rij AM, Jones GT, Hill GB, Jiang P. Neovascularization and recurrent varicose veins: more histologic and ultrasound evidence J Vas Surg 2004; 40: 296-302.

Chapter 5

Randomized clinical trial comparing endovenous laser ablation with cryostripping for varicose veins: 2 year results

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Background:
The aim of this randomized single centre trial was to compare the 2-year results of endovenous laser ablation (EVLA) and cryostripping for varicose veins.

Methods:
Hundred-twenty patients with CEAP clinical class C2, E1, AS3, Pr venous disease were equally randomized to one of two groups. Principal outcomes measures were freedom from recurrence, improvement in the venous clinical severity score (VCSS) and the Aberdeen Varicose Vein Severity Score (AVVSS) 6, 12, and 24 months after treatment.

Results:
Two-years life table analysis showed overall freedom from varicose veins recurrence in 77.4 per cent of patients (95 per cent CI; 71.7–78.0) in the EVLA group and in 66.0 per cent of patients (95 per cent CI 60.0-67.4) in the cryostripping group (P=0.2531). Scores for VCSS and AVVSS had improved significantly after treatment but the differences between the groups were not significant. EVLA provide significantly more favourable results than cryostripping with regard to operative time, post procedural pain, induration, activity impairment, and patient satisfaction,

Conclusion:
In this study, both EVLA and cryostripping were effective in patients with varicose veins, but patients favoured EVLA because of better cosmetic results, lower rates of postoperative morbidity, activity impairment, and recurrence rates up to 2 years. Registration number: ISRCTN33832691 (http://www.controled-trials.com).

Key words:
endovenous laser ablation, cryostripping, great saphenous vein.

Introduction

The standard treatment for patients with varicose veins due to reflux in the great saphenous vein (GSV) is ligation of the vein and its tributaries at the saphenofemoral junction (SFJ), followed by stripping of the GSV from the groin to just below the knee. The operation, which is often performed under general or spinal anaesthesia, is a day-care procedure that does not require specific instrumentation. Disadvantages of GSV stripping include the risks associated with anaesthesia, complications of saphenous nerve injury, haematoma, wound infection., For surgical stripping the literature suggested that approximately 20 per cent of patients would have reverse flow in the GSV at 3 months[1-3]. Since its introduction, we use cryostripping for varicose veins because it is less traumatic to the patient, is associates with lower rates of postoperative morbidity and has complications not worse than those of traditional surgery[4, 5].

Recently, endovenous laser ablation (EVLA) has been introduced to eliminate reflux by obliterating the GSV[6]. With EVLA, an 810-nm diode laser is passed into the GSV, and the heat generated by laser light absorption by blood destroys the intima and denatures collagen in the media, causing fibrotic occlusion of the vein[7]. Duplex imaging is required to access the GSV, to confirm the position of the laser fibre at the SFJ, and to assist with infiltration of tumescent local anesthesia. Such approaches hold the promise of being less invasiveness, and having fewer adverse effects, and of causing less impairment of activities, a greater improvement in quality of life (QOL) and a superior or equal outcome. Mundy et al[13], reported in systematic review 87-90 per cent occlusion of the GSV and abolition of reflux. But, these benefits need to be balanced against the more expensive equipment used in endovenous laser ablation.

The aim of this randomized clinical trial was to compare the 2-year results of patients with varicose veins due to reflux in the great saphenous vein, treated by endovenous laser ablation or cryostripping, performed by one consultant surgeon, in a single centre study. Details about the cost-effectiveness analyses of EVLA versus cryostripping will be published in a separate article.

Methods.

Consecutive patients with varicose veins, referred to our hospital from June 2003 to July 2005, were considered for inclusion in this study. The study protocol was approved by the regional ethics committee of the Mesos Medical Centre, Utrecht, The Netherlands.

The inclusion criteria were patients with primary symptomatic varicose veins, CEAP clinical class C2 venous disease[8], age 19–75 years, SFJ incompetence and great saphenous vein (GSV) reflux from the groin to below the knee, defined as retrograde flow lasting longer than 0.5 seconds on Duplex ultrasound imaging (ATL 3500 HDI, ATL ultrasound, Bothell, WA, USA). Reflux in perforator veins, tributaries at the saphenofemoral junction (SFJ), and accessory saphenous veins was defined as bidirectional flow. All patients fulfilling the inclusion criteria received written and verbal information about the aims and content of the study in accordance with the

Helsinki Declaration. After they had given written informed consent, 120 (17.6 per cent) of 681 patients considered for inclusion were randomized to either EVLA or cryostripping by means of numbered and sealed envelopes containing information about the type of treatment. (Fig 1) According to patient's preference, the interventions were performed, within 6 weeks of randomization, as day-care procedures (EVLA =38, cryostripping= 49) or outpatient procedures. (EVLA = 22, cryostripping = 11).

One consultant surgeon equally experienced in EVLA techniques and cryostripping performed all the procedures. All patients received low-molecular-weight heparin as thrombosis prophylaxis but prophylactic antibiotics were not used. The EVLA procedure has been described before.9 In brief, the GSV, 5 cm below the knee, was accessed under ultrasound guidance and the tip of the laser fibre was positioned 0.5 cm below the SFJ. Under ultrasound monitoring, 250 mL of tumescent local anaesthetic solution or Na CL 0.9 per cent, in case of no local anaesthesia, was administered within the facial sheath of the GSV. Manual compression was applied over the GSV while 14-Watt continuous laser energy (Diomed Inc, Andover, MA) was delivered at a pullback rate of 0.2 cm/s. Cryostripping consists of flush division of the GSV and all tributaries behind the second division, together with stripping of the GSV after catheterization with a flexible tip probe connected to a liquid nitrogen cryosurgery unit (Erbe, Tubingen, Germany). When the probe has reached the upper calf (5 cm below the knee) it is chilled to – 80 degrees C; cryocoagulation occurs within about 5 seconds. With the tip kept frozen, the probe is then steadily withdrawn with manual compression of the vein below the side of coagulation. This causes disruption of the vein, which is then stripped upwards to the groin, including avulsion of the tributaries. After EVLA and cryostripping, a graduated long compression stocking (20–30 mmHg) was worn day and night for 1 week. Aceclofenac , 100 mg twice daily for 1 week, was prescribed for postoperative pain. Patients were instructed to walk immediately after the procedure and were encouraged to resume normal activities and work as soon as possible. Six weeks after the procedure, persistent side branches were treated by liquid sclerotherapy or Muller phlebectomy with the intention of removing all varicosities.

A standard set of information was collected at each visit. Physicians completed the CEAP classification and the research fellow calculated the venous clinical severity score (VCSS)[10]. Scores for Aberdeen Varicose Vein Severity Score (AVVSS)[11] were recorded by the research fellow and calculated by the statistician. Perioperative information was collected about the operative time, defined as the duration of treatment: time of laser procedure versus time of cryostripping (skin to skin), the exact length of the extracted great saphenous vein and the ablated great saphenous vein. Postoperatively, information was collected about complications, activity impairment (defined as the percentage of patients at which 100 per cent daily activity resumed) and clinical improvement (a measure of patients satisfaction determined with a scale: scores ranged from +3 markedly improved, + 2 moderately improved, +1 minimally improved, no change to -3 markedly worse). Abolition of GSV reflux was demonstrated by its complete occlusion or obliteration, confirmed by Duplex ultra-

sound. Duplex-based recurrent varicose veins were classified in accordance with Stonebridge and have been described before[12]. Type 1 recurrences were those in which there was some residual connection between the superficial and deep systems, at or immediately around, the SFJ. These were further subdivided by the nature of the connection into three mutually exclusive subgroups: Type 1a, incompetent great saphenous vein; Type 1b, incompetent tributaries; Type 1c, neovascularization (defined as serpentine tributaries arising from the ligated SFJ. Type 2 recurrences were those in which there was no such connection: Type 2a, cross-groin connections; Type 2 b, thigh perforators.
Principal outcomes measures were freedom from recurrence, improvement in venous clinical severity score, and in the Aberdeen Varicose Vein Severity Score 6, 12, and 24 months after treatment.

Statistical analysis
A priori sample size calculations were based on detecting a 15 per cent difference in freedom from recurrence between the groups. With 80 per cent power at the 5 per cent significance level, 60 patients were required in each group. Analysis of outcome was on an intention to treat basis. Data from the assessments were coded and analyses were performed using SAS 9.1 statistical programs (SAS Institute, Cary NC, USA) and Microsoft® Excel (Microsoft Redmond, Washington, USA). Data are presented as the means ± standard deviation (or range) and percentage for count data unless indicated otherwise. The difference in primary outcome for EVLA versus cryostripping was assessed by means of log-rank test. Freedom from Duplex-based recurrence was graphically depicted by means of Kaplan-Meier curves, assuming the event took place exactly half-way between two follow-up visits. Fisher's exact test was used for secondary analyses and continuous variables and Student's t or Mann-Whitney test for continuous variables. Multivariate repeated measures general linear modelling was used to compare scores for venous severity scores, quality of life (QOL) and patient satisfaction over time. $P < 0.05$ was considered to indicate a statistical significant difference.

Results

Patient characteristics and Duplex outcomes at baseline are shown in Table 1. There were no conversions and the intended treatment was given to all patients. The mean energy delivered per length of vein was 57 (41-86) J/cm. Concomitant reflux in the small saphenous vein (SSV) was treated with saphenopopliteal ligation in 4 of the 120 limbs affected (3.3 per cent); 2 in each group. At 6 weeks residual side branches and accessory saphenous vein were detected in 37 (61.6 per cent) patients in the EVLA group and in 35 (58.3 per cent) patients in the cryostripping group (P= 0.8523). These patients requested and underwent liquid

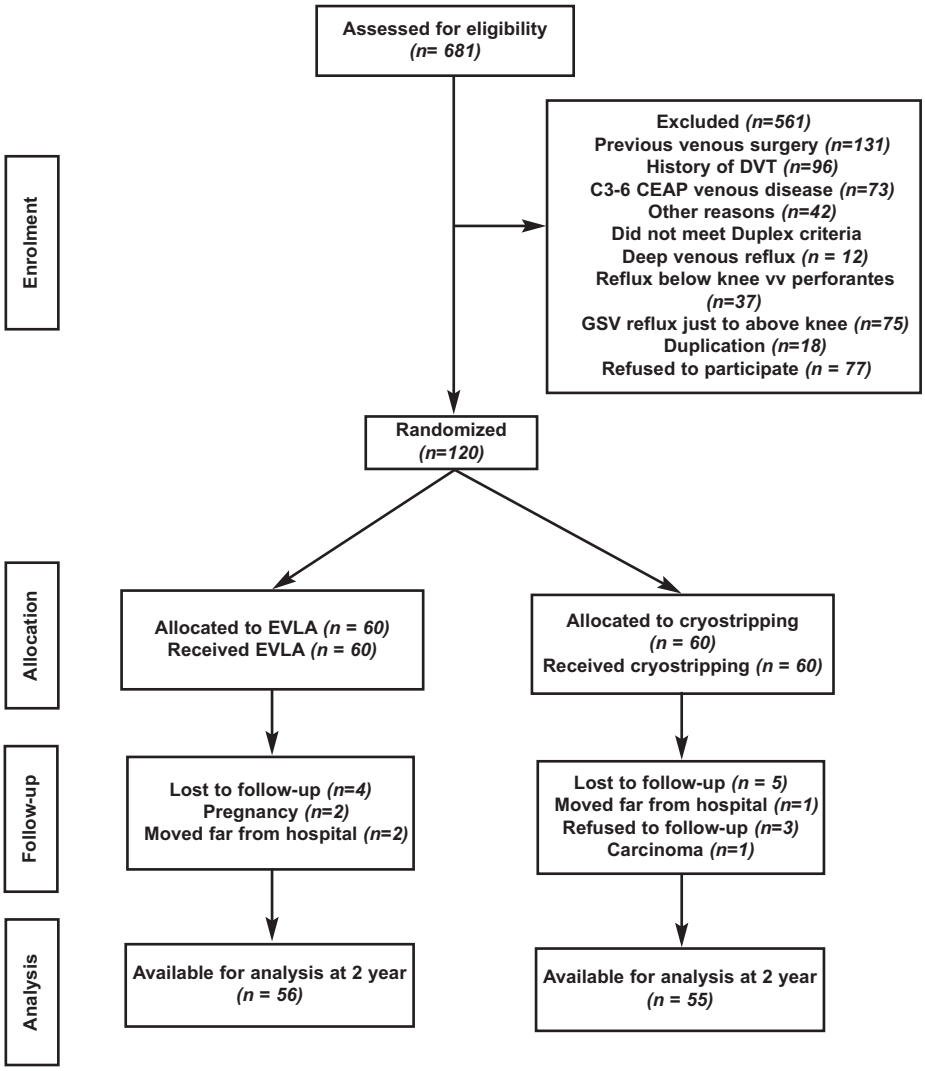

Fig 1 CONSORT flow chart. EVLA, endovenous laser ablation.

Table 1 Patient characteristics and duplex outcome at baseline.

	EVLA (n=60)	Cryostripping (n=60)	P-value
Sex ratio (F:M)	41:19	42:18	1.000
Age (years)*	46 (22-74)	49(19-73)	0.1515
Family history	28 (46.7)	38(63.3)	0.0980
Previous pregnancy	38(92.6 of women)	35(83.3 of women)	0.3126
In GSV at SFJ*			
Diameter (cm)	0.9 (0.4-1.7)	0.9 (0.5-1.6)	0.9564
Reflux time (s)	3.4 (0.5-6.0)	3.3 (0.5-6.4)	0.4380
In GSV 2 cm below SFJ*			
Diameter (cm)	1.01 (0.6-1.9)	0.93 (0.6-2.1)	0.1610
Reflux time (s)	3.72 (0.7- 6)	3.88 (0.5-6)	0.6189
Reflux(in one or more visible)			
SFJ tributaries	6/149(4.0)	7/157(4.5)	1.000
Above knee perforator veins	2/48 (4.2)	5/52 (9.6)	0.4388
Accessory saphenous vein	9/114(7.9)	100/114 (8.8)	1.000

* *Values are mean (range). Values in parentheses are percentages unless indicated otherwise. EVLA, endovenous laser ablation.*

sclerotherapy with aethoxysclerol 1% (EVLA n=36, cryostripping n=33) and Muller phlebectomy (EVLA n=1, cryostripping n=2). Follow-up at 6, 12 and 24 months was complete in 60 (100 per cent) patients, 58 (96.7 per cent) patients and 56 (93.3 per cent) patients in the EVLA group, respectively, and in 60 (100 per cent), 57(95 per cent) and 55 (91.6 per cent) patients in the cryostripping group, respectively. In 7 of 9 patients lost to follow up, ultra sound scanning did not detect evidence of recurrence in these patients. The 2 patients lost to follow-up at 6 months had improvement of VCSS and AVVSS, but refused duplex ultrasound scanning.

The differences between the groups significantly favoured EVLA with regard to the mean operative time (17 minutes (10-27) for EVLA and 24 minutes (15-60) for cryostripping, P=<0.0001), pain score (2.9 (0-8) and 4.4(0-8.5), P=0.0026) , activity impairment (45(75%) and 27(45%), P=0.0014), and induration, defined as a palpabele string along the course of the GVS, (9 (15%) and 31 (52%), P=<0.0001). There was a statistical significant difference in mean vein length between the groups but this was of no clinical importance (42 cm (30-38) for EVLA and 40 (30-50): mean: 2 cm). There were no significant differences between the groups concerning bruising, superficial thrombophlebitis, and saphenous neuralgia, determined by reported symptoms. (Table 2) Superficial groin infection occurred in 3 patients (5.0 per cent)

in the cryostripping group, 1 of whom needed additional wound care. Patients satisfaction (i.e., markedly +3) was 64.3 per cent for EVLA and 32.7 per cent for cryostripping, (P=0.0012) at the 2 year follow-up (Table 3).

Table 2 Post-procedural complications, pain score and activity impairment.

	EVLA (n =60)	Cryostripping (n=60)	P
Complications			
DVT	0	0	
Superficial thrombophlebitis	4 (6.7)	6(10)	0.7430
Bruising	55(91.6)	56(93.3)	1.000
Tightness	17	0	<0.0001
Skin burns	0	0	
Induration	9(15)	31(51.6)	<0.0001
Saphenous neuralgia	3 (5)	4 (6.7)	1.000
Wound complications	0	3	0.2437
Absence of pain	15 (25)	4 (6)	0.0109
Pain score *	2.9 (0-8)	4.4 (0-8.5)	0.0026
Normal physical activity	45(75)	27 (45)	0.0014

*Values are mean (range). Values in parentheses are percentages. EVLA, endovenous laser ablation.

In the EVLA group, the GSV segment was ablated completely in 57 (95.0 per cent) patients. Type 1a recurrence requiring additional SFJ ligation at the 6-months follow-up occurred in 3 patients. Type 1B recurrence (anterior saphenous vein n = 5, posterior saphenous vein n=1) occurred in 6 patients. Type 2b recurrence occurred in 2 patients. Type 1B and Type 2b recurrences were treated with sclerotherapy. In the cryostripping group, the introduction of the flexible tip probe in the below knee GSV was successful in all patients, and the GSV was stripped completely in 60 patients. Type 1C recurrence occurred in 11 patients (at 12 months n = 7 limbs, 24 months n = 4) and Type 2B recurrence occurred in 6 patients. All recurrences where treated with sclerotherapy. During follow-up, small saphenous vein recurrence requiring saphenopopliteal ligation occurred in 2 patients in each group. At the 12- and 24-months follow-up, recanalization of the GSV or the GSV tract was not observed in either group. Two-years life table analysis showed overall freedom from varicose veins recurrence in 77.4 per cent of patients (95 per cent CI; 71.7–78.0) in the EVLA group and in 66.0 per cent of patients (95 per cent CI 60.0-67.4) in the cryostripping group, P=0.2531) (Table 4).

Venous clinical severity scores improved significantly after treatment, but the differences between the groups were not significant. The most pronounced improvement in the venous clinical severity components “pain” and “varicosity” was observed at 6 months (pain 1.1 (0-3) to 0.2 (0-1) for EVLA and 1.2 (0-3) to 0.3 (0-1) for cryostripping: varicosity 2.1(0-3) to 0.8 (0-1) for EVLA and 2.1(0-3) to 0.7 (0-1) for cryostripping).The venous clinical severity score decreased with time, but the differences between the groups were not significant.

Table 3 Patients satisfaction.

	6 month EVLA (n=60) Cryostripping (n=60)	**1 year** EVLA (n=58) Cryostripping (n=57)	**2 year** EVLA (n=56) Cryostripping (n=55)
Markedly improved			
EVLA	24	35	36
Cryostripping	16	23	18
Moderately improved			
EVLA	31	23	20
Cryostripping	40	33	34
Minimally improved			
EVLA	1	0	0
Cryostripping	4	1	3
No change			
EVLA	4	0	0
Cryostripping	0	0	0
Minimally worse			
EVLA	0	0	0
Cryostripping	0	0	0
Moderately worse			
EVLA	0	0	0
Cryostripping	0	0	0
Markedly worse			
EVLA	0	0	0
Cryostripping	0	0	0

EVLA, endovenous laser ablation.

Table 4 Recurrent varicose veins up to 2 years after treatment demonstrated at duplex ultrasound.

	6 month EVLA (n=60) Cryostripping (n=60)	**1 year** EVLA (n=58) Cryostripping (n=57)	**2 year** EVLA (n=56) Cryostripping (n=55)
Type 1a recurrence			
EVLA	3	0	0
Cryostripping	0	0	0
Type 1b recurrence			
EVLA	1	3	2
Cryostripping	0	0	0
Type 1c recurrence			
EVLA	0	0	0
Cryostripping	0	7	4
Type 2a recurrence			
EVLA	0	0	0
Cryostripping	0	0	0
Type 2b recurrence			
EVLA	0	0	2
Cryostripping	0	2	4
Small saphenous vein			
EVLA	0	1	1
Cryostripping	0	1	1
Freedom from recurrence **			
EVLA	56 (93)	52 (86)	47 (77)
Cryostripping	60 (100)	50 (82)	41 (66)

*Type 1a: intact great saphenous vein (GSV). Type 1b: intact tributaries. Type 1c: neovascularization (defined as serpentine tributaries arising from the ligated sapheno-femoral junction. Type 2a: cross groin connections. Type 2 b: thigh perforators. EVLA, endovenous laser ablation. ** calculated with Kaplan Meier life table analysis*

Over the total study period, AVVSS scores decreased to a mean value of 5.2 for EVLA and to 4.5 for cryostripping, representing a 67 per cent improvement from baseline in both groups. (P=0.3280). In both groups, 51 patients showed an improvement of disease-specific QOL from baseline.(Table 5)

Table 5 Venous severity scores (VCSS) and Aberdeen Varicose Vein Severity Score (AVVSS) to 2 years after treatment with either EVLA or cryostripping

	Baseline EVLA (n=60) Cryostripping (n=60)	**6 months** EVLA (n=60) Cryostripping (n=60)	**1 year** EVLA (n=58) Cryostripping (n=57)	**2 years** EVLA (n=56) Cryostripping (n=55)	**p-value#**
VCSS*					
ELA	3.2 (0-6)	1.0 (0-3)	0.7 (0-4)	0.6 (0-4)	0.5607
Cryostrip.	3.4 (0-6)	1.0 (0-3)	0.9 (0-2)	0.8 (0-2)	
AVVSS					
EVLA	15.8(1.9-42.9)	5.6 (0-20.3)	5.4 (0-27.1)	5.2 (0-25.6)	0.0637
Cryostrip.	13.6(0.8-37.2)	6.2 (0-29.3)	7.0 (0-31.6)	4.5 (0.2-19.0)	

**Values are mean (range). VCSS, venous clinical severity score. AVVSS, aberdeen varicose vein severity score. EVLA, endovenous laser ablation. # EVLA versus cryostripping p-value for different effect over time (time* treatment interaction)*

Discussion

Recently, minimally invasive procedures were introduced as alternative for the surgical treatment of varicose veins. These procedures were designed to minimize the discomfort and complications associated with traditional surgery. The relative simplicity and high patient satisfaction associated [9,15] with these procedures made them increasingly popular, but proper clinical evaluation with adequate follow-up in a randomized trial is essential for implementing new techniques.

The present study reported the 2 years results of a randomized clinical trial comparing EVLA of the great saphenous vein with cryostripping. The patients in both groups were young, healthy adults with uncomplicated varicose veins (C2 CEAP classification). The patients themselves and personnel involved with the study were not blinded to the method used due to scarring in the groin (lack of blinding). We think that the risk of bias was reduced because important outcome variables such as VCSS and AVVSS were patient-reported measures. To eliminate technical factors influencing the outcome of treatment, a single centre study was performed with one consultant surgeon equally experienced in both techniques, and with no prefe-

rence. For EVLA, a standard laser delivery protocol was used resulting in an average energy deposition of 57 (range 41-86) J/cm treated vein. For cryostripping, a flexible tip probe was used allowing stripping the GSV, from below the knee upward to the groin. No long-term randomized clinical studies comparing EVLA and cryostripping have been published, and evidence on the choice of best intervention is lacking.

The operation time was significant shorter with EVLA (17 min. versus 24 min.) mostly because in cryostripping, a groin incision is necessary and time consuming. Ablated vein length was shorter in cryostripping but this was of no clinical importance (42 cm versus 40 cm, mean: 2 cm). Absence of pain and pain score was significant lower after EVLA. Pain is common after EVLA and cryostripping procedures but usually resolves in most patients after 2 weeks; however the relevance of post procedural pain should not be underestimated since is affects well-being and normal daily activity. In EVLA, most pain complaints are due to tightness of the treated above knee GSV segment, caused by acute inflammation with transverse and longitudinal retraction of the vein and seems not to be correlated with the laser energy used.[9] In contrast, pain after cryostripping might be caused by the freezing process and by damage to the surrounding tissue[5].

The frequency of adverse effect was low and not different between the groups, apart from induration, which was more frequent in the cryostripping group. The proportion of patients with bruising in both groups was comparable with that in the literature[13]. One patient in the cryostripping group needed treatment for a groin infect. No severe complications (e.g. deep vein thrombosis and pulmonary embolism) were observed in either treatment groups. Cryostripping favoured EVLA slightly with regard to ablation of the great saphenous vein. No operations failed in the cryostripping group and in the EVLA group three GSV segments reopened at 6 months follow-up. Our GSV occlusion rate of 95 (57/60) per cent after EVLA is consistent with published rates of 80-100 per cent of limbs[16-20]. In the three failed procedures in the EVLA group, the mean amount of energy delivered was 48.3 J/cm, 50.1 J/cm, and 47.6 J/cm, respectively, and lower than the suggested lower energy threshold of 70 J/cm[20]. Both procedures have significantly improved patient satisfaction, venous clinical severity and AVVSS scores and the improvement persisted up 2 years. The improvement of quality of life after treatment, in combination with the VCSS improvement highlights, that both EVLA and cryostripping are equally effective in abolition of GSV reflux and improving venous systems. Several authors have reported on the beneficial effect of varicose vein surgery on QOL[19,21].

Groin recurrence due to incompetent anterior accessory saphenous occurred in 6 limbs (10%) after EVLA alone but in none (0%) after cryostripping. Reflux in SFJ tributaries such as the anterior accessory saphenous vein is an important cause of recurrence [23,24]. In this study, of 228 visible accessory saphenous veins (superficial, anterior and posterior) at preoperative Duplex scanning, 19 (8.3%) had reflux; these were treated with sclerotherapy 6 weeks after treatment. Non-refluxing accessory veins were found in 208 limbs at Duplex scanning, of which only 6 (2.9%) resulted in recurrence. In accordance with Theivacumar[29], non-refluxing accessory

saphenous veins should not be treated at initial therapy because they do not have an adverse effect on outcome 2 years after EVLA.
However, a tendency was observed that cryostripping resulted in a poorer long term outcome because of neovascularization (Type 1C recurrence). Glass[23] described healing angiogenesis induced by the groin wound as a major source of new channels reconnecting superficial veins to the deep femoral vein around a ligated SFJ. Thus, interference with the venous drainage of the lower abdominal and pudendal veins may promote new vessel formation. According to van Rij et al[24], neovascularization is the major cause for duplex-confirmed recurrence of reflux in the groin after adequate surgery. Recent studies[25-28], have shown that SFJ ligation may be of little advantage after effective endovenous procedures and that neovascularization is more frequent after surgical treatment.
In conclusion, while both EVLA and cryostripping were effective in patients with varicose veins at the 2 year follow-up, EVLA provide significantly more favourable results than cryostripping with regard to operative time, post procedural pain, induration, activity impairment, patient satisfaction, and not significantly with regard to complications and freedom from recurrence Scores for VCSS and AVVSS improved significantly after treatment but the differences between the groups were not significant.

References

1. Sarin S, Scurr JH, Coleridge Smith PD. Assessment of stripping the long saphenous vein in the treatment of primary varicose veins. Br J Surg 1992; 79: 889-893.
2. Dwerryhouse S, Davies B, Harradine K, Earnshaw JJ. Stripping of the long saphenous vein reduces the rate of re-operation for recurrent varicose veins: five year results of a randomized trial. J Vas Surg 1999; 29(4):589-592.
3. Wintertborn RJ, Foy C, Earnshaw JL. Causes of varicose vein recurrence: Late results of a randomized trial of stripping of the long saphenous vein. J Vasc Surg 2004; 40:634-639.
4. Menyhei G, Gyevnar Z, Arato E, Kelemen O and Kollar L. Conventional stripping versus cryostripping: a prospective randomized trial to compare improvement in Quality of life and complications. Eur J Vasc Endovasc Surg 2008;35:218-223.
5. Schouten R, Mollen RM, Kuipers HC. A Comparison between cryosurgery and conventional stripping in varicose vein surgery: perioperative features and complications. Ann Vasc Surg 2006; 20:306-311.
6. Boné C. Tratamiento endoluminal de las varices con laser de diode studio preliminary. Rev Patol Vasc 1999; 5: 35-46.
7. Disselhoff BC, Rem AI, Verdaasdonk RM, der Kinderen DJ,Moll FL. Endovenous laser ablation: an experimental study on the mechanism of action. Phlebology 2008;23:69-76.
8. Porter JM, Moneta GL. Reporting standards in venous disease: an update. International consensus committee on chronic venous disease. J Vasc Surg 1999; 21:635-645.
9. Disselhoff BC, der Kinderen DJ. Moll FL. Is there recanalization of the great saphenous vein 2 years after endovenous laser treatment. J Endovasc Ther 2005; 12:731-738.
10. Ruhterford RB, Padberg FT, Comerota AJ, Kistner RL et al. Venous severity scoring: an adjunct to venous outcome assessment. J Vasc Surg 2000; 31:1307-1312.
11. Garrat AM, Macdonald LM, Ruta DA et al. Towards measurements of outcome for patients with varicose veins. Qual Health Care 1993; 2:5-10.
12. Stonebridge PA, Chalmers N, Beggs I, Bradburry AW et al. Recurrent varicose veins: a varicographic analysis leading to a new practical classification. Br J Surg 1995; 82 (1); 60-62.
13. Mundy L, Merlin TL, Fitridge RA, Hiller JE. Systematic review of endovenous laser treatment for varicose veins. Br J Surg 2005; 92:1189-1194.
14. Min RJ, Khilnani N, Zimmet SE. Endovenous laser treatment of saphenous vein reflux: long term results. J Vasc Interv Radiol 2003; 14:991-996.
15. Perkowski P, Ravi R, Gowda RCN, Olsen D et al. Endovenous laser ablation of the saphenous vein for treatment of venous insufficiency and varicose veins: early results from a large single center experience. J Endovasc Ther. 2004Apr; 11(2):132-138.

16. Proebstle TM, Krummenauer F, Gul D, Knop J. Nonocclusion and early reopening of the great saphenous vein after endovenous laser treatment is fluence dependent. Dermatol Surg 2004; 30(2): 174-178.
17. Timperman PE, Sichlau M, and Ryu RK. Greater energy delivery improves treatment success of endovenous laser treatment of incompetent saphenous veins. J Vasc Interv Radiol. 2004; 15:1061-1063.
18. Proebstle TM, Moehler T, Herdeman S. Reduced recanalization rates of the great saphenous vein after endovenous laser treatment with increased energy dosing: definition of a threshold for the endovenous fluence equivalent. J Vasc Surg 2006; 44:834-839.
19. Michaels JA, Brazier JE, Campbell WB, Macintyre et al. Randomized clinical trial comparing surgery with conservative treatment for uncomplicated varicose veins. B J Surg 2006; 93:175-181.
20. Theivacumar NS, Dellagrammaticas D, Beale RJ, Mavor AID and Gough MJ. Factors influence the effectiveness of endovenous laser ablation in the treatment of great saphenous vein reflux. Eur J Vasc Endovasc Surg 2008;35:119-123.
21. Mackenzie RK, Paisley A, Allan PL, Lee AJ et al. The effect of long saphenous vein stripping on quality of life. J Vasc Surg 2002; 35:1197-1203.
22. Mekako AL, Hatfield J, Bryce J, Lee D et al. A non randomized controlled trial of endovenous laser therapy and surgery in the treatment of varicose veins. Ann Vasc Surg 2006; 20: 451-417.
23. Glass GM. Neovascularization in recurrence of the varicose great saphenous vein following transaction. Phlebology 1987;2:81-91
24. van Rij AM, Jones GT, Hill GB, Jiang P. Neovascularization and recurrent varicose veins: more histologic and ultrasound evidence J Vas Surg 2004; 40: 296-302.
25. Chandler JG, Pichot O, Sessa C et al. Defining the role of extended saphenofemoral junction ligation: a prospective comparative study. J Vasc Surg 2000; 32:941-953
26. Ravi R, Rodriquez-Lopez JA, Trayler EA, Barrett DA et al. Endovenous ablation of incompetent saphenous vein: a large single-centre experience. J Endovasc Ther 2006; 13: 244-248
27. Disselhoff BC,der Kinderen DJ, Kelder JC and Moll FL. Randomized clinical trial comparing endovenous laser ablation of the great saphenous vein with and without ligation of the saphenofemoral junction: 2-year results. Submitted for publication.
28. Kianfard B, Holdstock JM, Whiteley MS. Radiofrequency ablation (VNUS closure®) does not cause neovascularization at the groin at one year: results of a case controlled study. Surg 2006(4);2: 71-74.
29. Theivacumar NS, Dellagrammaticas D, Beale RJ, Mavor AI et al. Fate and clinical significance of saphenofemoral junction tributaries following endovenous laser ablation of great saphenous vein. Br J Surg 2007;94:722-725.

Chapter 6

Randomized comparison of costs and cost-effectiveness of cryostripping and endovenous laser ablation for varicose veins: 2 year results

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Background:
Although endovenous laser ablation (EVLA) has essentially replaced surgical stripping, proper economic evaluation with adequate follow in a randomized clinical trial is important for considered policy decisions regarding the implementation of new techniques.

Methods:
Data from a randomized controlled trial comparing cryostripping and EVLA in 120 patients were combined to study Short Form (SF) 6D outcome, costs, and cost-effectiveness 2 years after treatment. Incremental cost per quality adjusted life year (QALY) gained 2 years after treatment was calculated using different strategies and uncertainty was assessed with bootstrapping.

Results:
QALY (SF-6D) was 1.59 (95% CI, 1.53-1.64) in patients who underwent cryostripping and 1.60 (95% CI 1.55-1.64) in patients who underwent EVLA 2 years after treatment. Cryostripping costs € 2651 per patient (95 % CI 2501-2820) and EVLA € 2783 (95% CI 2638-2937). Bootstrapping indicated that cryostripping was associated with an incremental cost-effectiveness ratio of € 32 (95 % CI -240-173) QALY gained. With regard to different strategies, outpatient cryostripping appeared the dominant strategy, i.e. was less costly and more effective 2 years after treatment.

Conclusion:
In this study, In terms of costs per QALY (SF-6D) gained outpatient cryostripping appeared to be the dominant strategy, but EVLA yielded comparable outcomes for a relatively little additional cost. Registration number: ISRCTN33832691 (http://www.controlled-trials.com).

Key words:
endovenous laser, cryostripping, costs and cost-effectiveness.

Introduction

Endovenous laser ablation (EVLA) was introduced as an alternative to the surgical treatment of varicose veins. The apparent simplicity and high patient satisfaction of this procedure has resulted in its fast dissemination of the technique despite lack of evidence regarding the balance between costs and effects. Several authors[1-3] have claimed that EVLA is as effective as surgical stripping, but with lower rates of post-operative morbidity and activity impairment and with recurrence rates not worse than those of surgical stripping. However, these benefits need to be balanced against the more expensive equipment required for EVLA. Proper economic evaluation with adequate follow up in a randomized clinical trial provides information to support considered decisions-making regarding the implementation of new techniques. Ultimately, the goal is to provide evidence for a new guideline on the standard of treatment for varicose veins.

This article describes a comparison of costs and cost-effectiveness based on the randomized controlled trial comparing the 2-year results of cryostripping and EVLA in patients with primary varicose veins due to great saphenous vein reflux.

Patients and Methods.

An economic analysis was carried out alongside a randomized clinical trial (RCT) comparing cryostripping and EVLA for varicose veins. The design and methods of this RCT have been described elsewhere[2]. In brief, patients with primary symptomatic varicose veins, CEAP clinical class C2 venous disease[4], who gave informed consent, were between 19–75 years, and had great saphenous vein (GSV) reflux from the groin to below the knee were randomly assigned, using numbered and sealed envelopes, to two treatment groups (n=60 in each group). According to patient preference, the procedures were performed as day-care procedures with conduction or general anaesthesia or as outpatient procedures with local anaesthesia. At 6 weeks, residual varicose veins were treated with sclerotherapy or Muller phlebectomy. At the 6-, 12- and 24- month follow-up, additional procedures such as saphenofemoral ligation, saphenopopliteal ligation, sclerotherapy, and Muller phlebectomy were recorded.

The principal outcome measure for this study was clinical effectiveness at 2 year, as measured using the Short Form (SF) 6D. The SF-6D is a single preference-based measure of health representing overall quality of life derived from the Short form (SF) 36 health status questionnaire[5], using the method described by Brazier et al[6]. Utility scores for the SF-6D were recorded at baseline and at 6-, 12–, and 24- month follow-up. The SF-6D results in a numeric score that represent heath state. A value of 1 represents the best health state, and 0 represents death. Using linear interpolation for the periods between measurements we calculated the quality adjusted life years (SF-6D) until 2 years after treatment by determining the individual area under the curve.

In the Netherlands, one-sided day-care stripping of the GSV with a disposable vein stripper, costs € 1888 and one-sided outpatient treatments cost € 1571. These costs are based on guideline prices according to the Dutch College Rates of Health,

(HTTP://www.ctg-zaio.nl) and are estimated treatment costs per patient. The costs of cryostripping and endovenous laser are similar, except for additional equipment. Although, the real costs of cryostripping and endovenous laser do not fully agree the estimated costs, we accepted these prices because we performed a comparative study. In order to perform cryostripping, a cryoapparatus (Erbe Benelux, Werkendam, The Netherlands) had been purchased for € 6667. Equipment depreciation and interest costs were calculated, resulting in an additional cost per cryostripping procedure of € 6. Additional costs for the probes and nitrogen tank were approximately € 48 per patient, resulting in a total outpatient treatment cost of € 1625 per patient and day-care treatment cost of € 1942 per patient. In the case of EVLA, a laser apparatus (Diomed D 15, Diomed Inc, Andover, MA) and a duplex ultrasound (Sonosite 180 plus, Sonosite, Bothell, WA) had been purchased for € 31568 and € 23940 resulting in additional equipment cost per EVLA of approximately € 26 and € 20. Additional costs for EVLA were a sterile procedure laser kit of € 314 per patient, resulting in total outpatient treatment cost of € 1931 per patient and total day-care treatment cost of € 2248 per patient. So, additional costs per EVLA were € 306 compared to cryostripping. During the study period, additional outpatient treatment costs were: saphenofemoral or saphenopopliteal ligation € 1571, sclerotherapy € 453 and Muller phlebectomy € 996 per patient, respectively. These costs were also based on guideline prices according to the Dutch College Rates of Health. The number of days of sick leave was recorded and the cost of lost productivity loss was based on the friction cost method[7], by which production loss over time is estimated by assuming that loss in production will be restricted to a period needed for the employer to adapt to the fact that the patient is absent (the friction period). This friction period was 123 days in 2003-2004, implying that absence from work beyond 123 days would not lead to a further loss of productivity. Productivity loss was fixed at a mean of 80 % of € 41 per hour.

For the economic evaluation, the estimates of QALY (SF-6D) gained at the 2 year follow-up were chosen as the primary measure of effect. The balance between costs and effects of cryostripping and EVLA was expressed in terms of incremental costs per QALY gained. The incremental cots-effectiveness ratio was calculated by dividing the difference in costs during the 2-year period by the difference in QALY's. A negative incremental cost-effectiveness ratio may imply a negative cost difference (cost savings) and positive health effects, or a positive cost difference (extra costs) and negative health effects. Likewise, positive incremental cost-effectiveness ratios may be obtained by positive cost differences and positive health effects or negative cost differences and negative health effects. To assess the robustness of the results of the RCT we repeated the comparisons for different strategies: inpatients treatment, outpatient treatment, and outpatient treatment in combination with a 50% reduced price for the EVLA kit (from € 314 to € 157).

Statistical analysis

All economic analyses were carried out on an intention- to- treat principle. Data on outcomes were collected before and 6, 12, and 24 month after treatment.

Incomplete questionnaires were returned for completion. Costs and health outcomes were analysed using SAS® version 9.1.3 (SAS Inc, Cary, NC) and Microsoft® Excel databases (Microsoft, Redmond, Washington, USA). Data are presented as means with 95 % confidence intervals (CI) unless indicated otherwise. Cost effectiveness planes where used to depict the joint distribution of incremental costs and effects where incremental costs are on the Y-axis and incremental effects were on the x-axis. The uncertainty regarding the results were assessed using bootstrapping (n=500), in which the original data were used to provide an empirical estimate of the sampling distribution through repeated resampling from the observed data8. T-test was used for comparison of results with normal distribution. The Mann-Whitney U test was used for comparison of skewed data. The significance level was set at $P < 0.050$.

Results

The clinical results of the randomized controlled trail have been reported elsewhere[2]. Briefly, between June 2003 and July 2005, 120 patients were equally randomized to cryostripping or EVLA. Baseline characteristics of the patients and great saphenous veins are given in Table 1. Follow-up at 24 months was complete for 55 (91.6 per cent) patients who underwent cryostripping and for 56 (93.3 per cent) patients who underwent EVLA. No additional procedures were performed and no lost working days were recorded for the patients lost to follow-up patients (n=9, 7.5 %).

Characteristics	**Cryostripping** (n=60)	**Endovenous laser** (n=60)
Sex ratio (F:M)	42:18	41:19
Age (years)*	49(19-73)	46 (22-74)
Occupation		
Unoccupied	10	13
Light physical work	19	22
Medium physical work	18	18
Heavy physical work	3	1
Retired	10	6
In GSV 2 cm below SFJ*		
Diameter (cm)	0.93 (0.6-2.1)	1.01 (0.6-1.9)
Reflux time (s)	3.88 (0.5-6)	3.72 (0.7- 6)

Table 1 Baseline characteristics

** Values are presented as means (range). Values in parentheses are percentages unless indicated otherwise. GSV, great saphenous vein. SFJ, saphenofemoral junction.*

Patients preferred day-care treatment with conduction or general anaesthesia in 49 (81.7 %) cryostripping procedures and in 38 (66.3 %) EVLA procedures. Ipsilateral saphenopopliteal junction (SPJ) ligations was performed in 4 limbs at the first treatment (cryostripping outpatient n=1, cryostripping day-care n=1; EVLA outpatient n=1, EVLA day-care n=1). None of the patients had in hospital complications or needed re-operations. Three wound complications occurred in the cryostripping group but the influence of these complications was limited; one patient needed additional wound care. At 6 weeks, residual side branches were treated with aethoxysclerol 1% sclerotherapy (cryostripping n=33, EVLA n=36) and Muller phlebectomy (cryostripping n=2, EVLA n=1). During follow-up, recurrent varicose vein detected on Duplex ultrasound and requiring additional treatment were recorded in 19 (31.7 per cent) patients who underwent cryostripping (SPJ ligation n=2, sclerotherapy n=17), and in 13 (21.7 per cent) patients who underwent EVLA (SFJ ligation n=3, sclerotherapy n=8, SPJ ligation n=2). No lost working days were recorded for the patients with recurrent varicose veins requiring additional treatment.
Over the total study period, mean SF-6D scores improved slightly from 0.78 (sd 0.11) at baseline to 0.80 (sd 0.11) at 2 year for patients who underwent cryostripping and from 0.77 (0.11) to 0.79 (0.12) for patients who underwent EVLA, representing a 2.5% and 2.6 % improvement from baseline, respectively. The quality adjusted SF-6D, calculated in terms of quality adjusted life years by determining the individual area under the curve, was 1.59 (95% CI, 1.53-1.64) QALY for patient who underwent cryostripping and 1.60 QALY (95% CI 1.55-1.64) for patients who underwent EVLA at 2-year follow up.

Table 2 provides details of the costs of cryostripping and EVLA during the 2-year follow-up. The costs of day-care treatment were higher because of the higher costs of the operating room and the costs of hospitality stay. Additional equipment costs were higher in the EVLA group because of significantly higher charges of the purchase and depreciation of the laser apparatus and the duplex ultrasound machine Disposables were significantly more expensive in the EVLA group and in particular, the use of the EVLA kit was a cost-driver. Patients in the cryostripping group returned to work after 2.2 (0-14) days on average and in the EVLA group after 1.3 (range 0-6) days on average, respectively (P=0.1256). The cost of lost productivity was € 17812 in the cryostripping group and € 10262 in the EVLA group. Self-employed patients were significantly more likely than employees to return to work directly. In the cryostripping group 11 of 12 (91.7 per cent) self-employed people returned to work directly and 8 of 27 (29.6 per cent) of people in paid employment: in the EVLA group the data were 7of 7 (100 percent) and 19 of 33 (76.6 per cent). No lost working days were recorded for the patients during follow up.

Table 2 Costs (€) of cryostripping and endovenous laser until 2 years after treatment.

	Cryostripping (n=60)	**Endovenous** laser(n=60)
Costs of initial treatment		
Initial treatment	109793	106306
Additional equipment*	3460	21600
Total costs initial treatment	113253	127906
Costs of additional treatment		
Additional procedures at 6 weeks		
Muller Phlebectomy	1992	996
Sclerotherapy	14949	16308
Additional procedures during F.U.		
Adjunctive SFJ ligation	0	4713
Sclerotherapy	7701	3624
Phlebectomy	0	0
Small saphenous vein ligation	3142	3142
Total costs of additional treatment	27784	28783
Costs from sick leave		
Proportion in work	40	41
Direct return to work	19	26
Costs of sick leave	17812	10262
Total costs of treatment	**158849**	**166951**

**costs included depreciation, interest and annual maintenance.*

The results of bootstrapping and the subsequent strategies comparing day-care treatment, outpatient treatment, and outpatient treatment in combination with 50% reduced price of EVLA kit are presented in Table 3. Comparing cryostripping and EVLA, the cost-effectiveness ratio (€/QALY) gained was in favour of cryostripping: 1730 (95% CI 1591-1891) versus 1760 (95% CI 1633-1898). With regard to different strategies, and in terms of cost-effectiveness ratio (€/QALY) gained outpatient cryostripping appeared to be the better strategy, i.e. was less costly and more effective 2 years after treatment. Comparing outpatients and 50% reduced price

Table 3 Costs (€), QALY (SF-6D) gained, and cost-effectiveness ratios (€/QALY) for cryostripping and endovenous laser, and for the subsequent strategy analysis..

	Cryostripping		Endovenous laser		P-value
	mean	95 % CI*	mean	95 % CI*	
All patients					
Costs	2651	2501-2820	2783	2638-2937	0.234
QALY	1.59	1.53-1.64	1.60	1.55-1.64	0.824
Cost-effectiveness ratio	1730	1591-1891	1760	1633-1898	0.788
Day-care					
Costs	2663	2503-2849	2804	2647-2980	0.272
QALY	1.58	1.51-1.65	1.61	1.54-1.68	0.628
Cost-effectiveness ratio	1758	1595-1972	1748	1603-1913	0.934
Outpatient					
Costs	2595	2158-3104	2746	2491-3043	0.566
QALY	1.61	1.51-1.69	1.58	1.51-1651	0.594
Cost-effectiveness ratio	1623	1317-1920	1783	1561-2003	0.406
Outpatient, and 50% reduced price of EVLA kit					
Costs	2595	2158-3104	2586	2331-2883	0.982
QALY	1.61	1.51-1.69	1.58	1.51-1.65	0.594
Cost-effectiveness ratio	1623	1317-1920	1681	1462-1898	0.770

*Values are mean. QALY; quality adjusted life year. * bootstrapping 95 % confidence interval. An accurate estimate of the absolute and pertaining 95% CI was obtained using 500 bootstrapping replications of the trial.*

for the EVLA kit, the cost-effectiveness ratio (€/QALY) was still in favour of outpatient cryostripping but only a limited difference remained: 1623 (95% CI 1317-1920) for outpatient cryostripping € 1681 (95 % CI 1462-1898) for outpatient EVLA outpatients and 50% reduced price for the EVLA kit. The results of bootstrapping and the incremental costs-effectiveness ratio are presented in Table 4. The incremental costs-effectiveness ratio was in favour of outpatient cryostripping; 148 (95 CI -524-257) €/QALY at 2-year follow-up.

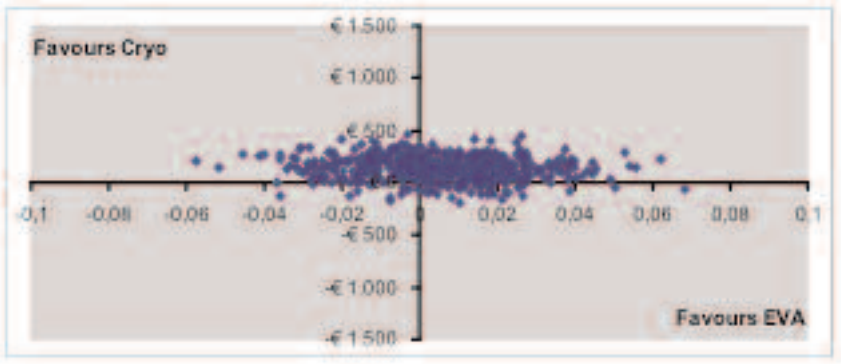
Table 4 Incremental cots-effectiveness ratio at 2 year

	Incremental cost-effectiveness (€/QALY)	95 CI %*
All patients	-32	-240 - 173
Day-care patients	9	-251- 276
Outpatients	-148	-524 - 257
Outpatient, 50% reduced EVLA kit	-46	-421- 358

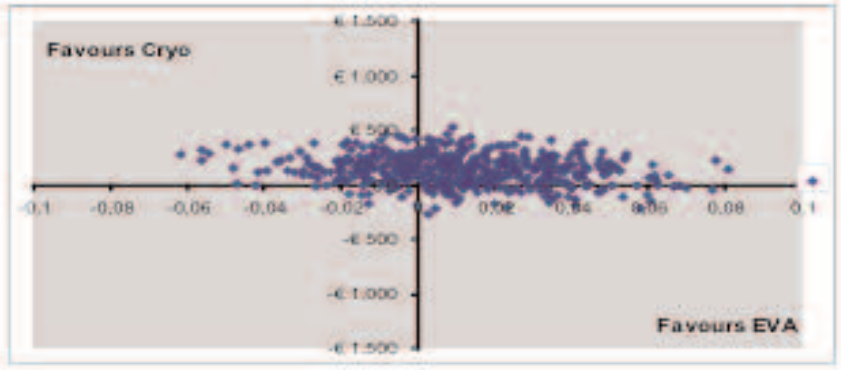
*QALY, quality of life years (SF-6D). * bootstrapping 95 % confidence interval. An accurate estimate of the absolute and pertaining 95% CI was obtained using 500 bootstrapping replications of the trial.*

Results of the bootstrapping and the subsequent strategies are depicted in cost-effectiveness planes in Fig 1. The QALY (SF-6D) gained panel (Fig 1A) showed that most replicas (53%) lie in the right upper quadrant indicating that EVLA yielded a better outcome in terms of QALY and was more expensive. For day-care treatment (fig1B) most replicas lie in the right upper quadrant indicating that EVLA was more effective and more costly. In case of outpatient treatment (Fig1C) most replicas lie in the left upper quadrant indicating that cryostripping was more effective and less costly. For 50 % reduced EVLA kit and outpatient treatment (fig1 D) most replicas were in the left lower upper quadrant indicating that cryostripping was more effective and less costly.

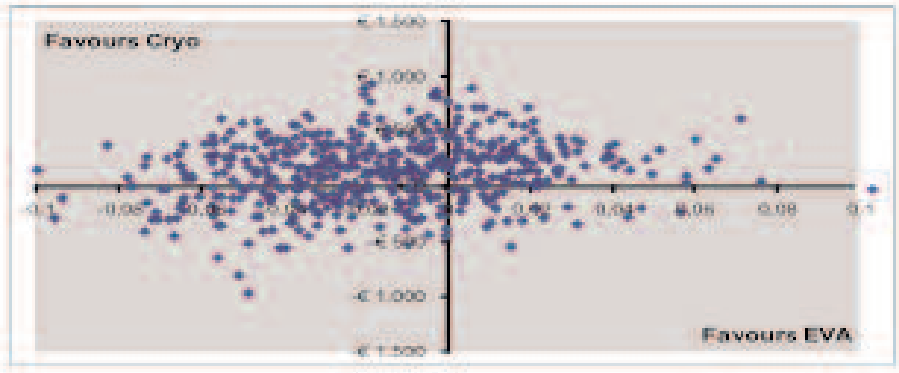
A= all patients. Cryostripping and EVLA: incremental costs (€) and gain QALY (SF- 6D) over 2 years



B= Day-care. Cryostripping and EVLA: incremental costs (€) and gain QALY (SF-6D) over 2 years



C=outpatients, Cryostripping and EVLA: incremental costs (€) and gain QALY (SF-6D) over 2 years



D = outpatients and 50 % reduced EVLA kit. Cryostripping and EVLA: incremental costs (€) and gain QALY (SF-6D) over 2 years.

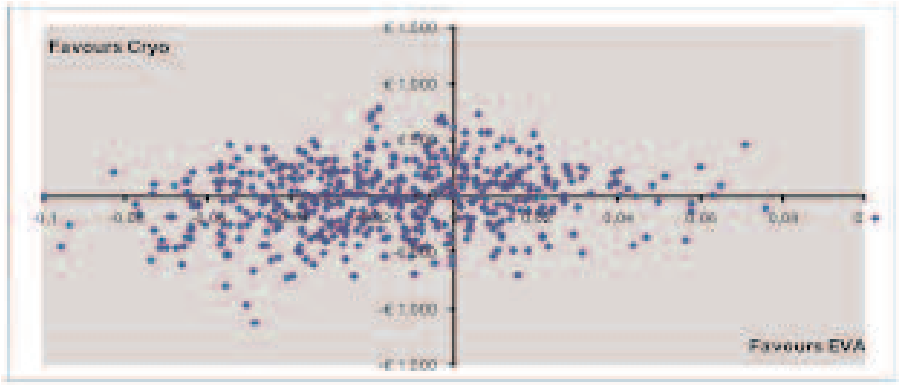


Fig 1 Cost-effectiveness planes of cryostripping and endovenous laser (EVLA) for A: all patients, B: day-care strategy, C: outpatient strategy, D: outpatient and 50% reduces price of laser kit. The cost-effectiveness plane consists of four quadrants. A dot to the left of the Y-axis means that cryostripping yields a better outcome, whereas a dot to the right means the endovenous laser yields a better outcome. Likewise a dot above the x-axis means that the costs of EVLA are higher, whereas a dot below the x– axis means that cryostripping is more expensive. The upper left and the lower right and upper left quadrant would indicate that both costs and effects are favourable (dominant) for cryostripping and EVLA respectively.

Discussion

This study compared the costs and cost-effectiveness of cryostripping and EVLA with a follow-up of 2 years. The results indicates that for patients with varicose veins and great saphenous vein reflux, outpatient cryostripping appeared to be the dominant strategy In terms of costs per QALY (SF-6D) gained, but EVLA yielded comparable outcomes for a relatively little additional cost. While the time to return to work and costs of lost productivity were in favour of EVLA, the total costs of EVLA were higher than those for cryostripping.

To out knowledge, the presented study is the first, to report on the economic evaluation of a randomized clinical trial comparing cryostripping and EVLA with a 2 year follow-up. The patients in both groups were young, healthy adults with uncomplicated varicose veins (C2EpAS3Pr CEAP classification). To eliminate technical factors influencing the outcome of treatment, we performed a single centre study with one consultant surgeon equally experienced in both techniques, and with no preference. The results of the clinical trial indicated that cryostripping and EVLA were equally effective in patients with varicose veins, but that patients favoured EVLA because of better cosmetic results, lower rates of postoperative morbidity, and lower rates of activity impairment up to 2 years. The results are comparable to recent published findings[1,3]. In addition, we found no significant differences between the groups regarding clinical outcome measured with SF-6 6D scores.

In the present cost comparison, the cost of the laser apparatus, fibre kit and the Duplex ultrasound were major factors that increased the costs of EVLA group. In contrast, hospital stay and anaesthesia (conduction or general) were important factors that increased the cost of cryostripping. Day-care procedures significantly increased the cost of both interventions. Sick leave was shorter than that reported in other studies[1,3,9], probably because we included relatively many self-employed patients who were significantly more likely to return to work directly than employees. The cost of lost productivity increased the cost of cryostripping (€ 17812 versus € 10262) and accounted for 13.6% (versus 7.4%). of the total cost of treatment. The proportion and costs of additional procedures performed 6 weeks after treatment and during the follow-up period were comparable: € 27784 for cryostripping and € 28783 for EVLA and accounted for 17.3 per cent and 17.5 per cent of the total cost of treatment, respectively. When comparing day-care and outpatient procedures, we found the incremental costs-effectiveness ratio to be in favour of outpatient cryostripping. In the Netherland, the costs for day-care or outpatient treatment are independent of the operative technique. This means that reducing additional costs will overcome the cost disadvantage of EVLA. When we compared outpatient cryostripping with outpatient EVLA and 50 % reduced EVLA kit, the cost-effectiveness ratio was 1623 (95% CI 1317-1920) €/QALY for cryostripping and 1681 (95 % CI 1547-1744) €/QALY for outpatient EVLA, only a limited difference remaining of 46 €/QALY. In conclusion, the outcome of cryostripping and endovenous laser is similar. In terms of costs per QALY (SF-6D) gained outpatient cryostripping appeared to be the dominant strategy, but EVLA yielded comparable outcomes for a relatively little additional cost. Although sick leave is shorter with EVLA, overall this procedure is more

expensive than cryostripping. Until the prices of endovenous laser equipment decreases, outpatient cryostripping be the dominant procedure of choice on economic perspectives even though patients favoured EVLA because of better cosmetic results, lower rates of postoperative morbidity, and lower rates of activity impairment.

References

1. Rasmussen LH, Bjoern L, Lawaetz M, Blemings A et al. Randomized trial comparing endovenous laser ablation of the great saphenous vein with high ligation and stripping in patients with varicose veins: shirt-term results. J Vasc Surg 2007;46:308-315.
2. B.C. Disselhoff, D.J. der Kinderen, J.C. Kelder, and F.L. Moll. Randomized clinical trial comparing endovenous laser ablation with cryostripping for varicose veins: 2 year results. Submitted for publication.
3. Darwoord RJ, Theivacumar N, Dellagrammaticas D, Mavor AI et al. Randomized clinical trial comparing endovenous laser ablation with surgery for the treatment of primary great saphenous varicose veins. Br J Surg 2008 Mar; 95(3):294-301
4. Porter JM, Moneta GL. Reporting standards in venous disease: an update. International consensus committee on chronic venous disease. J Vasc Surg 1999; 21:635-645.
5. Garrat AM, Macdonald LM, Ruta DA et al. Towards measurements of outcome for patients with varicose veins. Qual Health Care 1993; 2:5-10.
6. Brazier J, Roberts J, deveril M. The estimation of a prefenece based measure of health from the SF-26. J health Econ 2002; 21:271-292
7. Koopmanschap MA, Rutten FF, van Ineveld BM van Roijen L. The friction cost method for measuring indirect costs of disease. J Health Econ 1995; 14:171-189.
8. Efron.B, Tibshirani RJ. An introduction in the bootstrap. New York, NY: Chapman & Hall; 2003.
9. Mundy L, Merlin TL, Fitridge RA, Hiller JE. Systematic review of endovenous laser treatment for varicose veins. Br J Surg 2005; 92:1189-1194.

Chapter 7

Is there a risk for lymphatic complications after endovenous laser treatment versus cryostripping of the great saphenous vein? A prospective study

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Objective:
To investigate whether lymphatic complications occur after endovenous laser treatment (EVLA) versus cryostripping.

Methods:
A prospective analysis of patients who underwent lymphoscintigraphy before and 6 months after treatment of primary varicose veins.

Results:
Of 120 patients randomized in a clinical trial comparing EVLA and cryostripping, 33 agreed to participate in this study. Six months after treatment, none of the 17 patients treated with EVLA and 1 (6.3%) of the 16 patients treated with cryostripping had clinical grade 1 lymphoedema, with marked disruption of the lymphatics around the knee. This patient also showed an abnormal uptake of radioactive tracer at the groin, 120 minutes after injection.

Conclusion:
This study demonstrated that no lymphatic complications occurred 6 months after EVLA whereas one lymphatic complication occurred after cryostripping, however not in the groin but at the knee.

Key words:
great saphenous vein, endovenous laser treatment, lymphatic complications

Introduction

Endovenous laser treatment (EVLA), a new minimally invasive percutaneous procedure to treat varicose veins due to reflux in the great saphenous vein (GSV), was introduced by Boné.[1] The procedure is based on laser-induced damage to the wall of the saphenous vein. An 810-nm diode laser is passed into the GSV, and the heat generated by light from the laser destroys the intima and denatures collagen in the media, causing fibrotic occlusion of the vein. Complications of EVLA include bruising, cutaneous paraesthesia, and skin burns[2-4].

To date, no data have been reported on the occurrence of lymphatic complications of EVLA. While lymphatic complications after surgery for varicose veins have been reported, objective data are limited[5-11]. Lymphoscintigraphy is a well-tolerated and reliable test to determine whether the lymphatic system is normal. It provides images of the lymphatics and lymph nodes, and allows dynamic evaluation of lymph transport[12-16]. The aim of this prospective study was to investigate whether lymphatic complications occur after EVLA versus cryostripping.

Patients and methods

The study was carried out from March 2003 to February 2005 and in conjunction with a randomized controlled trial comparing EVLA and cryostripping of the GSV for the treatment of varicose veins. All patients underwent clinical evaluation, venous duplex ultrasonography, and lymphoscintigraphy. The inclusion criterion was CEAP clinical class C2, E1, AS3, Pr primary symptomatic venous disease[17]. Exclusion criteria were previous lower limb, abdominal and varicose vein surgery, a history of suspected or manifest lymphoedema clinical grade 1-3[18], deep vein thrombosis, active or healed leg ulceration, history of acute infection (cellulites and/or lymphangitis), pregnancy, peripheral arterial disease, and lack of fluency in Dutch. Written informed consent was obtained from all patients.

Lymphatic system evaluation

The lymphatic system was evaluated by means of lymphoscintigraphy 2-4 weeks before and 6 months after treatment according to our clinic's protocol. Human albumin colloid (Nanocolloid), obtained from Amersham Health, UK was labelled with Technetium-99m pertechnetate (Tc-99m) according to the manufacturer's instructions. Directly after subcutaneous injection of 74 MBq Tc-99m nanocolloid into the interdigital space between the first and second and between the second and third toes of both feet (37 MBq in 0.1 mL in each foot), image acquisition was started with the patient in supine position and the gamma camera positioned over both feet (A). The gamma camera (Siemens ecam, Erlangen) was equipped with low-energy high-resolution collimators. After completion of the static image (6 sec), a dynamic series of images (6 frames acquired over 5 minutes) was recorded with the pubic symphysis in the middle of the field-of-view. Thereafter, the patient was encouraged to walk around for about 1 hour. Delayed imaging was performed 2 hours after injection of the tracer. A 1 minute static image with the pubic symphysis in the middle of the field-of-view (B) was recorded, immediately followed by 5 minute static images of the pelvic area, thighs, knee area and lower legs (C). Experienced nuclear physicians, who had no knowledge of patients' status, independently interpreted the scintigrams. Quantification of lymphatic flow was performed according to the equation: counts B x 1/C / counts A x 6 sec./ 60 sec. x 100%. Diagnostic for lymphoedema at 2 hours was less then 14.2 ± 4 2 % in the groin quantification of tracer.

Treatment
The same surgeon, who was experienced in varicose vein surgery and EVLA, performed all procedures. Treatment was performed under local, regional or general anaesthesia, whichever the patient preferred. According to our clinic's protocol, all patients received low-molecular-weight heparin as thrombosis prophylaxis. Prophylactic antibiotics were not used. No adjunctive procedures were performed at the time of surgery. After the procedure, a graduated compression stocking, e.g. 20-30 mmHg, was worn day and night for 1 week. Non-steroidal anti-inflammatory drugs, 100 mg twice daily for 1 week, were prescribed for postoperative pain. Patients were instructed to walk immediately after the procedure and were encouraged to resume normal activities and work as soon as possible. Six weeks after the procedure, residual varicose veins were treated by compression sclerotherapy (CST) and /or multiple phlebectomies.

Endovenous laser treatment
The EVLA procedure has been described previously[4]. In brief, the GSV was accessed 5 cm below the knee, under ultrasound guidance. A 0.035" J-tip guide wire was introduced through the needle. After removal of the needle, a 45-cm 5 French introducer sheath was placed into the GSV over the J-tip guide wire and the internal dilator and guide wire were removed. Intraluminal position was confirmed by aspiration of blood. The tip of the sheath was positioned 1-2 cm below the saphenofemoral junction under ultrasound guidance. A 600-Ìm core bare tip fibre, connected to the Diomed D15 surgical diode laser (Diomed Inc, Andover, MA), was inserted into the sheath. Under ultrasound monitoring, 200-250 mL of tumescent local anaesthetic (200 mL physiological saline (0.9%), 40 mL lidocaine (1%), and adrenaline (1: 100,000) neutralized with 10 mL sodium bicarbonate (8.4%)) was administered within the facial sheath of the GSV to achieve analgesia, compression of the vein, and a heat sink. In the case of spinal anaesthesia 200-250 ml NaCl % was administered. The position of the fibre tip was confirmed by visualization of the red aiming beam of the laser at the saphenofemoral junction. Manual compression was applied over the GSV while 14 Watt continuous laser energy at 810-nm wavelength was delivered from 1-2 cm below the saphenofemoral junction to the access site below the knee.

Cryostripping.
The principle of cryostripping is ligation and division at the confluence of the GSV and its tributaries with the femoral vein at the level of the hiatus saphenous, followed by vein removal with a cryoprobe without distal incision. High ligation was performed through an incision (2-3 cm) in the groin. The external pudendal vein, the superficial epigastric vein, the superficial circumflex iliac vein, the anterior accessory of the GSV, and the posterior accessory of the GSV were identified, ligated, and divided. The saphenous vein was stitched through and divided flush at the saphenofemoral junction. Then, the saphenous vein was catheterized with a probe with a flexible tip connected to a liquid nitrogen cryosurgery unit (Erbe, Tubingen,

Germany). When the probe was below the knee (–5 cm), the tip of the probe was chilled by expansion of NO2, leading to temperatures of –850 C and freezing of the vein to the probe from the inside. With the tip kept frozen the probe was steadily withdrawn, causing disruption of the vein. The vein was then stripped upwards to the groin while the GSV was compressed above the site of coagulation. Wound closure was achieved with Ethilon (Johnson & Johnson, New Brunswick, New Jersey, USA)

Definitions and statistical analysis

Data were entered into an Excel spreadsheet (Microsoft, Redmond, WA, USA). Data are presented as means (± standard deviation) unless indicated otherwise.

Results

Of 120 patients randomized in the clinical trial comparing EVLA and cryostripping, 33 agreed to participate in this study. Table 1 shows the demographic and procedural data of the 17 patients who underwent EVLA and the 16 patients who underwent cryostripping. One of the patients who underwent cryostripping developed a haematoma in the groin but this did not require surgical treatment. Cellulitis, lymphangitis, lymphatic leaks, and lymphocoeles were not observed during the follow-up period. All patients had normal lymphoscintigraphic flow patterns and inguinal node uptake before treatment. Six months after treatment, none of the patients who underwent EVLA and 1 (6.3%) of the patients who underwent cryostripping had abnormal lymphoscintigraphy findings. This female patient, who did not have additional treatment at 6 weeks, had clinical lymphoedema grade 1, with marked disruption of the lymphatics at the knee.Tc-99m pertechnetate uptake at the groin, 120 minutes after injection, was 7.3 %. No adverse side effects were noted in the patients who underwent lymphoscintigraphy.

Table 1 Demographic and procedural data of 33 patients

	EVLA (n =17)	Cryostripping (n =16)
Sex ratio (F:M)	14:3	11:5
Age (years)	49.2 ± 11.7	47.8 ± 14.5
Height (m)	1.74 ± 0.10	1.76 ± 0.08
BMI < 25 kg/m2	16	16
Treated length vein (cm)	43.5 ± 3.3	44.1 ± 4.7
Anaesthesia		
Local	11	9
General	6	7
Mode of laser light delivery		
Continuous	13	
Intermittent	4	
Energy/vein (J/cm)	52.3 ± 13.3	-
Probe tip (flexible: straight)	-	15:1
Wound complications	-	1
Successful treatment	17	16
Additional treatment at 6 weeks		
Sclerotherapy	3	5
Multiple phlebectomies	0	0

Values are means ± standard deviation. BMI, body mass index.

Discussion

In this prospective study none of the 17 patients who underwent EVLA had lymphatic complications whereas one of 16 patients who underwent cryostripping had a lymphatic complication, however not in the groin region but at the level of the knee. She was treated with physiotherapy and compression stockings as required.

To our knowledge in 2003, there were no randomized controlled trial data available comparing the risk for lymphatic complications after surgical treatment in patients with symptomatic venous disease. So, a formal power calculation could not be performed. It was estimated that during a period of two years all symptomatic patients with CEAP clinical class C2, E1, AS3, Pr venous disease were invited to participate.

Despite the excellent regenerative capacity of the lymphatic system, lymphatic complications after varicose vein surgery do occur. Bergan[5] reported lymphocoeles to occur in 2.1 % of patients after varicose veins surgery and Timi et al[6] who used lymphoscintigraphy, observed lymphatic injury in 60 % of patients after venous stripping. Ouvry et al[7] reported that lymphatic complications occurred in about 0.9% of more than 184 000 patients operated for varicose veins, and van Bellen et al[8] found extensive lymphatic disruption in all seven patients following saphenous stripping from ankle to groin. They concluded that lymphatic disruption results from intraluminal stripping and extraluminal avulsion. Lymphatic complications are more common following re-exploration of the groin for recurrent varicose veins[10,11]. Hayden et al[10] reported on the outcome of direct and indirect exposure of the saphenofemoral junction for recurrent varicose veins. Overall, lymph leakage / lymphocoele occurred in 21 of 127 patients (16.5%). In contrast, “short” saphenous stripping and inversion stripping techniques reduce the likelihood of lymphatic disruption because the calf lymphatics and the extraluminal tissue are not damaged[11].

To date, there are no data on lymphatic complications after minimally invasive procedures such as EVLA, radiofrequency obliteration, and duplex-guided foam sclerotherapy. In EVLA, in contrast to surgical stripping, the saphenous vein is approached via a puncture below the knee rather than in the groin. The saphenous vein is damaged by light from a laser introduced into the GSV, under perivenous infiltration of anaesthetic. Although temperatures at the tip of the laser fibre exceeding 1200 ^{O}C have been reported, heat conduction into surrounding tissue is limited[19]. The use of perivenous infiltration contributes to reduce the risk of extraluminal thermal damage[20].

Secondary lymphoedema of the lower extremity has a reported frequency of 10% to 49%[14] and is characterized by obstruction. It is caused by surgical trauma, recurrent infection and malignancy. However, it is unusual for surgery alone to cause lymphoedema, because the lymphatic system has excellent regenerative capabilities[15]. Lymphoedema secondary to venous disease such as deep vein thrombosis also may have a significant clinical role. Lymphoscintigraphy has emerged as the diagnostic test of choice in patients with suspected lymphoedema of the lower extremity. The technique, first introduced in 1953 by Sherman and Ter- Pergossian, is minimally invasive and without significant risk or discomfort to the patient. It provides

detailed information about the lymphatic anatomy and can be used to evaluate lymphatic function. However, the protocol for lymphoscintigraphy is not standardized and differs among diagnostic centres. Differences include the choice of radiotracer, the type and site of injection, and the use of dynamic and static acquisitions. Quantification of the regional lymph node accumulation of radiotracer is the preferred method for evaluating the lymphatic system and is more sensitive than qualitative lymphoscintigraphy for diagnosing lymphatic impairment. Weissleder et al[16] compared quantitative and qualitative lymphoscintigraphy and found that quantitative analysis detected lymphoedema in 100% of 308 extremities whereas qualitative analysis detected lymphoedema in only 70% of the extremities. The sensitivity of lymphoscintigraphy for identifying abnormal lymphatics in the leg is 73% to 97% and the specificity is 100%[15].

Up till now, it is unclear to what extent the disruption of superficial lymphatics may have in the formation of lymphoedema following venous surgery. Such disruption occurs, in particular after surgical stripping of the GSV for varicose veins, after harvesting of the GSV in combination with arterial bypass grafting, and after groin exploration for recurrent varicose veins. EVLA results in less trauma to the lower extremity, which probably minimizes the development of lymphatic complications.

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References

1. Boné C. Tratamiento endoluminal de las varices con laser de diode studio preliminary. Rev Patol Vasc. 1999; 5:35-46.
2. Min TJ, Khilmani NM. Endovenous laser ablation of varicose veins. J Cardiovasc Surg 2005; 46:395-405.
3. Sichlau MJ, Ruy RK. Cutaneous thermal injury after endovenous laser ablation of the great saphenous vein. J Vasc Interv Radiol 2004;15:865-867
4. B.C. Disselhoff, D.J. der Kinderen. F.L. Moll. Is there recanalization of the great saphenous vein 2 years after endovenous laser treatment?. JEVT. 2005; 12:731-738.
5. Bergan JJ. Surgical management of primary and recurrent varicose veins. In: Handbook of Venous Disorders. Gloviczki P, Yao J.(Eds), Chapman & Hall Medical, London 1996,394-415
6. Timi JR, Zanoni MF, Yamada AS et al. Lesions lymphatiques des membres inferieurs après chirurgie des varices. Analyse par lymphoscintigraphia. Revista Panamericana de Flebologia y Linfologia 31 (1998),17-21
7. Ouvry PA, Guenneguez H, Ouvry PA. Complications lymphatiques de la chirurgie des varices. Phelobolgy 1993 ;46(4) : 563-568.
8. van Bellen B, Gross WS, Verta MJ, Yao JS. Lymphatic disruption in varicose vein surgery. Surg 1977;82(2):257-259

9. Browse N, Burnand K , Lea Thomas M. Diseases of the vein: Pathology, Diagnosis and Treatment. London: Arnold, 1988:235
10. Hayden A, Holdsworth J. Complications following re-exploration of the groin for recurrent varicose veins. Ann R Coll Surg Engl 2001;83: 272-273
11. Critchley G, Handa A, Maw A and Harvey A et al. Complications of varicose vein surgery. Ann R Coll Surg Engl 1997;79:105-110.
12. Gloviczki P, Clacagno D, Schirger A, Pairolero PC et al. Non-invasive evaluation of the swollen extremity: experiences with 190 lymphoscintigraphic examinations. J Vasc Surg 1989 May; 9(5):683-639.
13. Cambria RA, Gloviczski P, Naessens JM, Wahner HW. Non-invasive evaluation of the lymphatic system with lymphoscintigraphy: a prospective semi-quantitative analysis in 386 extremities. J Vasc Surg 1993;18:773-782
14. Szuba A, Shin WS, Strauss W, Rockson S. The third circulation: radionuclide lymphoscintigraphy in the evaluation of lymphoedema. J Nucl Med 2003; 43-57
15. Tiwari A, Cheng K-S, Button M, Myint F et al. different diagnosis, investigation, and current treatment of lower lymphoedema. Arch Surg. 2003; 138:152-161
16. Weissleder H, Weissleder R. Lymphedema: evaluation of qualitative and quantitative lymphoscintigraphy in 238 patients. Radiology.1986;167:729-735
17. Porter JM, Moneta GL. Reporting standards in venous disease: an update. International consensus committee on chronic venous disease. J Vasc Surg. 1999; 21: 635-645.
18. Bergan JJ. Lymphoedema: pathophysiology, classification and clinical evaluation. In Gloviczki P, Yao J eds. Handbook of venous disorders. New York: Arnold, 2001; 453-458.
19. B.C. Disselhoff, A.I. Rem, R.M. Verdaasdonk, D.J. der Kinderen et al. Endovenous laser treatment: an experimental study on the mechanism of action. Phlebology 2003; (2): 69-76.
20. Beale RJ, Mavor AIDF, Gough MJ. Heat dissipation during endovenous laser treatment of varicose veins: is there a risk of nerve damage. Phlebology 2006;21(1):32-35

Chapter 8

Histological studies of the great saphenous vein below the knee after endovenous laser ablation

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Submitted for publication

Abstract

Objective:
To assess early pathological changes in the below-knee non-varicose great saphenous vein (GSV) and adjacent tissue after endovenous laser ablation (EVLA) in legs scheduled for below-knee amputation.

Methods:
The below-knee GSV in 6 patients was treated with EVLA using 14, 12, and 10-watt laser power, with continuous and intermittent laser exposure. Six segments (3 x 3 cm) of GSV and adjacent tissue were excised and examined histologically.

Results:
Histological evaluation revealed thermal damage of the endothelial layer of the intima, and carbonization and necrosis of the lumen side of the media at the site of the laser tip. Vascular perforation with subsequent perivascular bleeding was seen in a few cases treated with 40 80 J/cm and in all cases treated with 110 200 J/cm. The saphenous nerve was not damaged.

Conclusion:
in this study, EVLA of the below-knee GSV seemed to be a safe procedure.

Key words:
great saphenous vein, laser, and varicose veins.

Introduction

Endovenous laser ablation (EVLA) for the management of varicose veins is rapidly gaining acceptance and popularity among physicians and patients alike, and is becoming the new standard of treatment for reflux in the great and small saphenous vein[1]. Laser energy is intraluminal absorbed and converted into heat, which in turn gives rise to steam bubbles, as extensively described by Proebstle[2,3]. Intraluminal and extraluminal temperatures have been reported by Beale et al[4] and Disselhoff et al[5]. Because the mechanism of action and consequences of laser treatment have not yet been studied in detail, we studied the nature of the acute pathological damage to the distal part of the great saphenous vein (GSV) induced by EVLA in patients needing a below-knee amputation because of gangrene. We paid particular attention to whether the saphenous nerves that run alongside the GSV were damaged by EVLA.

Methods

Patients

Patients with irreversible lower limb tissue damage due to peripheral atherosclerotic obstructive vascular disease were invited to participate in the study. None of the patients had varicose veins or a history of chronic venous disease. Six patients (mean age 82 years, range 72–95 years; five females) were treated with EVLA of the below-knee GSV prior to amputation. The amount of energy delivered per centimetre vein is summarized in Table 1.

Table 1. Amount of energy delivered per cm treated vein

Patient	14 W(C)J/cm	14 W(I)J/cm	12 W(C)J/cm	12 W(I)J/cm	10 W(C)J/cm	10 W(I)J/cm
1	82	65	55	56	56	55
2	51	37	57	44	53	38
3	60	33	58	44	50	44
4	80	42	46	28	41	33
5	60	28	40	32	43	30
6	136	111	137	169	170	200
Mean	66.6 ±13.7	41.0 ±14.3	51.2 ± 7.9	40.8 ±11.1	48.6± 6.4	40.0 ±9.9

(C=continuous, I=intermittent)

EVLA procedure
All EVLA procedures were performed before below-knee amputation and with an intact circulation. All patients received low-molecular-weight heparin as thrombosis prophylaxis according to the standards of our clinic and were treated in supine position. The limb was prepared with digluconate 0.5% in alcohol 70% and draped. The GSV at the ankle was accessed via venesection. A 0.035" J tip guide wire was introduced through the needle. After removal of the needle, a 45 cm 5 French introducer sheath was placed into the GSV over the J tip guide wire and the internal dilator and guide wire were removed. Intraluminal position was confirmed by aspiration of blood. The tip of the sheath was positioned at the level of the anterior incision for Burgess's amputation. A 600 mm core, bare tip fibre, connected to the Diomed D15 surgical diode laser (Diomed Inc, Andover, MA), was inserted into the sheath. Approximately 100 ml normal saline was administered within the facial sheath of the GSV to achieve analgesia, compression of the vein, and a heat sink. The position of the fibre tip was confirmed by visualization of the red aiming beam of the laser at the upper incision. Manual compression was applied over the GSV while laser energy at 810 nm wavelength was delivered. The GSV below the knee was treated using 14, 12, and 10-watt laser power, delivering continuous and intermittent (1 s off and 1 s on) laser light with a manual pull-back rate of about 0.2 cm/s. One patient (nr 6) was treated with 14-watt laser power, continuous delivery and with different pull-back rates of 0.2 cm/s and 0.1 cm/s.

Histopathological methods
Six segments (3 x 3 cm) of treated GSV and adjacent tissue and 1 segment of non-treated GSV and adjacent skin and subcutaneous tissue were excised from the amputation specimen, resulting in 216 cross-sections of treated GSV and adjacent tissue and 6 cross-sections of non-treated GSV and adjacent tissue. These were fixed in formaldehyde solution 24% m/v buffered with 40 mmol phosphate buffer, pH =7. Four-micron sections were prepared and stained with standard haematoxylin-eosin and elastic-von Gieson stain.
Pathological changes in each segment were evaluated according to the following criteria: degree of carbonization, damage to the endothelium, and thermal lesions of the intima, media, and adventitia, perforation, effects on adjacent perivascular tissue in the area of laser treatment. Particular attention was given to the peripheral nerves accompanying the GSV.

Ethical approval
The local research ethics committee granted ethical approval for the study. All patients provided written informed consent.

Results of histopathological investigation

The intima was damaged, and the endothelium was destroyed or completely absent in all specimens examined. Carbonization was seen where the laser tip had touched the vein wall. The laser induced injury in the media closest to this carbonization was characterized by homogeneous basophilic discoloration and coagulation necrosis and loss of distinction between collagen and muscular bundles. Clumping and condensation of nuclear material was also observed in damaged tissue. In contrast, the deeper tissue showed minimal damage. Vein perforation was observed in a few cases treated with 40–80 J/cm, and in all cases treated with 110–200 J/cm, with extensive haemorrhage and haemolysis in and outside the vein extending into the surrounding subcutaneous tissue. Gas bubbles were seen in the haemorrhage outside the veins. Many black dots of carbonization were seen at the site of vein perforation. In areas of haemolysis steam bubbles were identified as empty holes. We observed many saphenous nerve fibres and side branches running adjacent to the GSV but in no case did we observe any damage to the nerves or perineural structures. No vein thrombosis, haemolyses, or vasa nervosum was noted in any of the specimens.

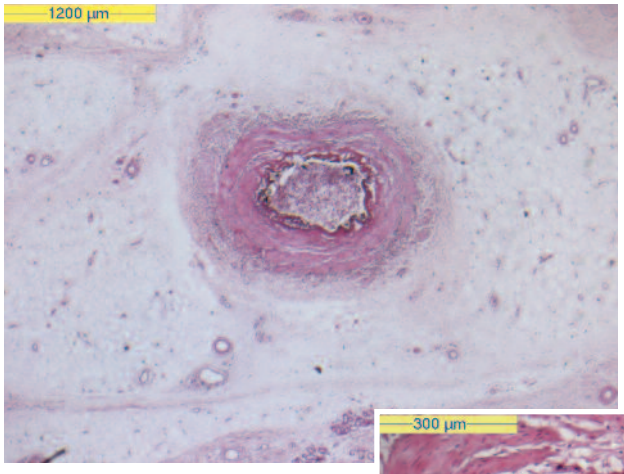
Discussion

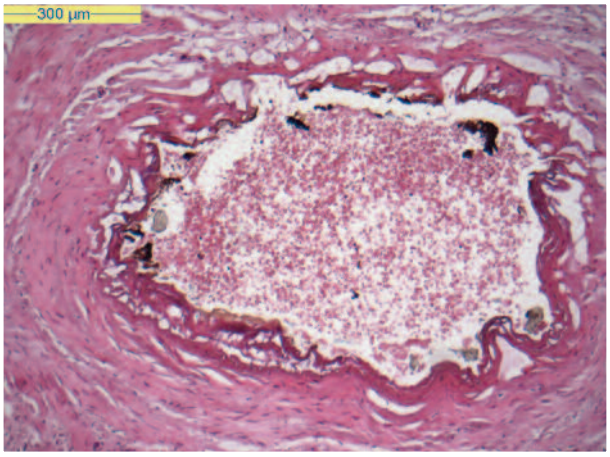
There has been hesitation to use EVLA for the treatment of incompetence of the GSV in the lower leg and for the treatment of the lesser saphenous vein at the calf because of the possibility of causing nerve damage (the saphenous nerve runs close to the GSV and lesser saphenous vein in the lower leg). This study shows that EVLA is a safe procedure with perivascular bleeding as the only complication, caused by puncturing of the vein wall by the laser tip. No other major pathological findings were observed, notably no damage to the perivascular nerve. If nerve damage is so unlikely, then EVLA treatment of the GSV below the knee and of the small saphenous vein may become possible.

Varicose veins are a common disorder, with the majority being caused by incompetence of the greater and small saphenous vein. Standard surgical treatment, high ligation and stripping, is accompanied by the potential need for general anaesthesia and is associated with nerve damage and a considerable down time for the patient. Endovenous laser therapy seems not to have these drawbacks. This explains its rapidly growing acceptance by both specialists and patients. Furthermore, patients treated with EVLA soon resume their daily activities, including work.

In an earlier histological study of vein specimens from the very proximal end of the GSV immediately after EVLA, the endothelium was found to be partially or completely damaged and vacuolization of the intima and media was observed[6]. We did not observe the latter. However, the treatment protocol used deviated from the standard EVLA protocol in that the endovenous procedure was repeated in the GSV until the surgeon felt, by retrograde pushing, that the optical fibre was being stopped and there was no tumescent anaesthesia. However, with the standard protocol, EVLA is performed as a single pass procedure under tumescent anaesthesia. In the study of Bush[7] et al., the standard protocol for EVLA was followed. Samples taken from the

GSV at the knee revealed the absence of the endothelial layer shortly after the procedure, deposition of fibrin in the vascular lumen at 6 weeks, and thrombus in a dilated vein with disrupted muscle and elastic tissue layers.
In the current study, samples were taken immediately after the laser procedure of the GSV in the lower leg, where the GSV has a smaller calibre and is in close proximity to the saphenous nerve and its side branches. Even in specimens in whom the GSV running alongside the saphenous nerve was perforated, nerve damage was not seen, which suggests that nerve damage is unlikely to occur with this procedure. We conclude that, based on this study, the rate of postoperative complications is expected to be low after EVLA of the below-knee GSV.





References

1. Min RJ, Khilnani N, Zimmet SE. Endovenous laser treatment of saphenous vein reflux: long term results. J Vasc Interv Radiol 2003; 14:991-996.
2. Proebstle TM, Lehr HA, Kargl A, EspinolaKlein C, Rother W, Berthge S et al. Endovenous treatment of the greater saphenous vein with a 940 nm diode laser: thrombotic occlusion after endoluminal thermal damage by laser generated steam bubbles J. Vasc.Surg 2002; 35(4): 729-736.
3. Proebstle TM, Sandhofer M, Kargl A, Gul D, Rother W, Knop J et al. Thermal damage of the inner vein wall during endovenous laser treatment: key role of energy absorption by intravascular blood. Dermatol. Surg 2002; 28(7): 596-600.
4. Beale RJ, Mavor AIDF, Gough MJ. Heat dissipation during endovenous laser treatment of varicose veins: is there a risk of nerve damage. Phlebology 2006; 21(1):32-35.
5. Disselhoff BC, der Kinderen DJ. Moll FL. Is there recanalization of the great saphenous vein2 years after endovenous laser treatment? JEVT. 2005; 12:731-738.
6. Corcos L Dini |S, de Anna D et al. The immediate effects of endovenous diode 808 nm laser in the greater saphenous vein: morphologic study and clinical implications J Vas Surg 2005; 41(6):1018-1024.
7. Bush RG, Shamma HN Hammong KA. 940 laser for treatment of saphenous insufficiency: histological analysis and long term follow up. Photomed Laser Surg 2005.23:15-19.

Chapter 9

General discussion and conclusions

Varicose veins are a common medical condition afflicting 25 % of women and 15 % of men[1]. Great saphenous vein (GSV) reflux is the most common underlying cause of varicose veins[2]. The traditional treatment for GSV reflux has been surgical removal of the GSV. However, surgery is associated with significant perioperative morbidity and the recurrence rates can be as high as 40% after 5 years[3,4].
Less invasive surgical treatments including high ligation of the GSV at saphenofemoral junction (SFJ) have been attempted in the hope that gravitational reflux would be controlled while preserving the vein for possible use as a bypass graft. Unfortunately, ligation of the GSV alone usually results in recurrent varicose veins[5]. Therefore, when GSV reflux is determined to be the principal underlying problem, treatment should aim to eliminate this source of reflux with ablation of the incompetent venous segment. In an attempt to reduce morbidity and to shorten the recovery time, several minimally invasive techniques have been developed as alternatives to surgery in the last few years. Endovenous laser ablation (EVLA) is one of the most promising of these techniques. This thesis describes experimental studies designed to understand the mechanism of action of endovenous laser and its evaluation in single-centre clinical studies.

Experimental studies

Mechanism of action.

In **Chapter 2** we describe the results of experimental studies of the mechanism of action of endovenous laser (EVLA). We study the absorption of laser light in blood, thermal effects in a blood-filled ex vivo human veins using an intravascular thermography catheter and heat dissipation in a model tissue using close up and thermal imaging techniques. Video images during laser exposure showed that laser light is absorbed by blood, resulting in the formation of a coagulum around the tip of the laser fibre. On continued laser exposure, the water in the blood vaporizes and the vapour (steam) bubbles appear to be incorporated into the coagulum, forming an insulating layer around the fibre tip. Laser light is then directly absorbed in the vapour-filled coagulum and blood dissociates, forming black patches in the coagulum, and burning onto the fibre tip. Furthermore, with regard to steam bubble formation, we observe a steady generation of steam bubbles in front of the fibre tip and escaping from the coagulum replacing the blood in the environment. The generation of steam requires a threshold laser emitted energy to heat up the blood until it reaches boiling temperature. The volume of laser-generated steam bubbles produces correlates directly to the amount of laser energy delivered. In this in vitro set-up, the thermocouples recorded variable intravascular temperatures. Laser-induced heat appeared to have a large gradient concentrated around the fibre tip. The temperature increases rapidly above carbonization temperatures (300 ºC) when the fibre tip reaches the thermocouple and remains these temperatures for a few second. The steam bubbles fill the lumen of the vessel around the fibre, exposing the vessel wall to 100 ºC for several seconds. After the vapour bubbles collapse, the temperature stays above 70 ºC for over 10 seconds and gradually decreases to the

environment temperature. These measurements are confirmed in the tissue model using thermal imaging techniques based on colour Schlieren techniques, showing the dynamics of heat dissipation around the fibre tip and into the model vessel wall. Thermal imaging in combination with temperature measurements shows that the mean temperature rise inside the channel of the tissue model is approximately 50^{0}C. The diffusion of heat to surrounding tissue is minimal, about 5 mm Thus, application of endovenous laser shows to be dominated by heterogeneously heating of the vessel wall by intraluminal expanding steam bubbles effectively created inside a coagulum of blood around the fibre tip. On average, the vessel is exposed for tens of seconds to temperatures of about 70 ^{0}C with only minimal dissipation of heat outside the vessel. Based on these observations we postulate a 4 phase model for the mechanism of action of EVLA as depicted in Figure 1.

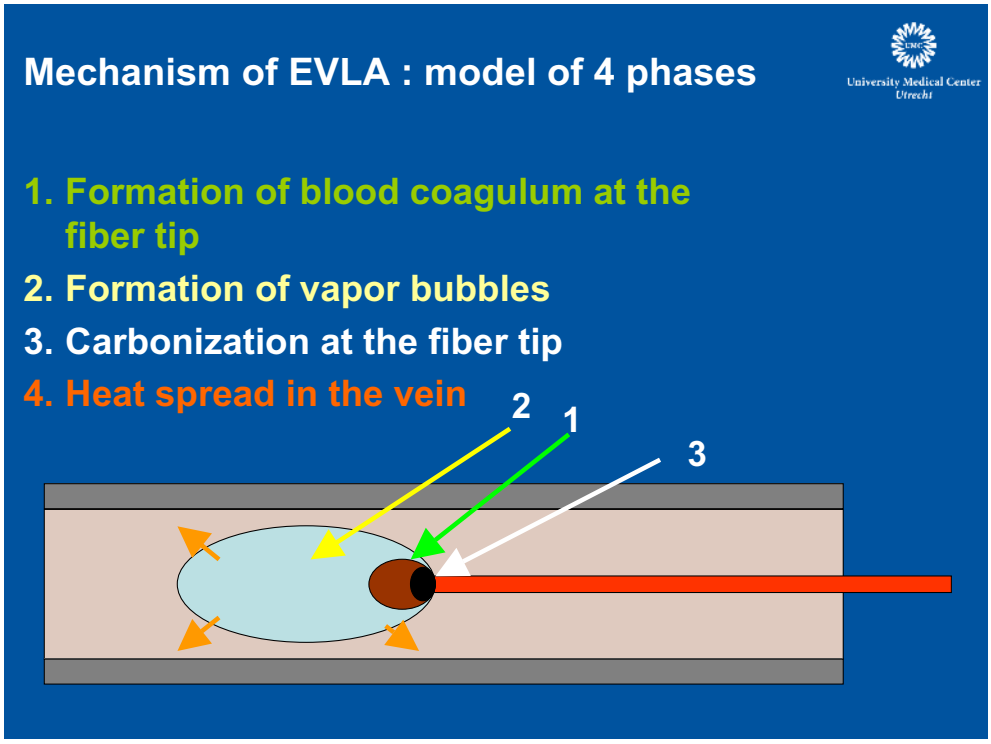


Fig.1 Four phase model for the mechanism of action of EVLA.

The observations in our in vitro studies are mostly confirmed by the observations in the clinical studies and histology harvested after treatment. In vivo, monitoring the vein during laser exposure using ultrasound, a continuous stream of echogenic vapour bubbles is observed. These steam bubbles are created at the fibre tip filling the lumen of the vein of a length of several centimetres and moving in downward direction (Figure 2).

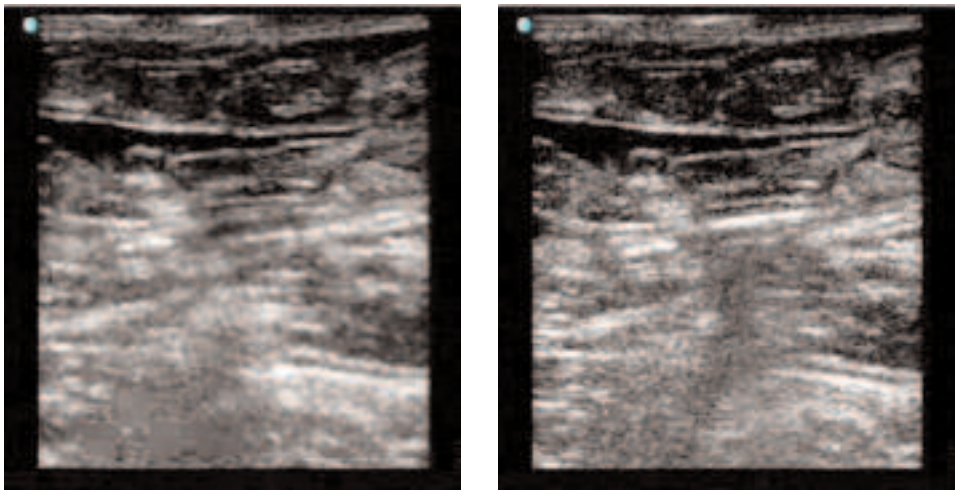


Fig. 2 Comparing the left and right ultrasound images captured during laser exposure, the echogenic steam bubbles filling the lumen of the vein over several centimetres can be clearly observed in the right frame.

We also investigate the histological effects of EVLA of the GSV. In **chapter 8** we described the early pathological changes induced by EVLA in the non-varicose below knee GSV and adjacent tissue in patients due to undergo below knee amputation. Different amounts of laser power and different modes of laser light delivery are used. We observe that the intima is damaged in all slides, and the endothelium is destroyed or complete absent in all the preparations examined. This is consistent with the finding that the lumen of the vessel is homogenously filled with steam bubbles (Figure 2). The laser induced damage to the media closest in the area of carbonization is characterized by homogeneous basophilic discoloration, coagulation necrosis and loss of distinction between collagen and muscular bundles. There is clumping and condensation of nuclear material. In contrast, the deeper tissue shows minimal damage. Vein perforation is seen in some veins treated with 40-80 J/cm, and in all veins treated with 110-200 J/cm with extensive haemorrhage and haemolysis being seen in and outside the vein, and extending into the surrounding subcutaneous tissue. Gaseous bubbles are seen in the haemorrhage outside the veins. Similar histological findings have been reported previously. Corcos et al[7] evaluates 29 proximal GSV segments that are excised immediately after ablation with an 808 nm laser. In these segments, the blood appears coagulated, vaporizes and carbonized. Necrosis of the vein wall is confined to the intimal layer. Damage to the intracellular structures is seen in the media and occasionally in the adventitia. Two specimens demonstrate perforation of the vein wall. Proebstle et al [8] reports a single patient who underwent excision of the GSV after EVLA. Macroscopically, the vein shows reddening, carbonization and areas of perforation. The energy is delivered in

an intermittent fashion, with direct contact between the laser fibre and the vein wall being associated with direct damage to the vein wall. Both authors suggest that permanent occlusion of the vein can only be obtained if EVLA causes thermal damage to the endothelium and intima. Severe damage to tissue with complete wall perforation may occur if the fibre tip comes in direct contact with the vessel wall[9]. Thus, histological evaluation reveals a large variation in the effect of EVLA on tissue, ranging from extensive tissue damage and vessel disruption to minor effect limited to the wall opposite the laser fibre.

In conclusion:
The mechanism of action of endovenous laser is attributed to laser induced endovenous steam bubble formation, indirectly heating the vein wall over a large area of the lumen, and partly direct heating of the vein wall as a consequence of closer contact between the fibre tip and the wall itself.

Which parameters influence the effectiveness of endovenous laser treatment?
The laser induced thermal reaction will vary depending on several laser parameters such as wavelength, the mode (continuous or intermittent) and amount of laser energy delivered, and treatment conditions such as pull back speed, local vein diameter, force exerted deforming the vessel shape, and the presence of blood during EVLA.

Laser source, wavelength and absorption spectra
EVLA refers specifically to the use of an 810 nm diode laser, although results for other wavelengths in the range of 810-1470 nm have also been reported. The energy from both the 810 nm and 980 nm lasers are mainly absorbed by blood, whereas the 1470 nm wavelength is absorbed in the same magnitude by water instead of blood and therefore more specifically targets the water component of soft tissue in the vein wall. The absorption of the dominant chromophores in vascular tissue is depicted in Figure 3 showing the blood and water dominant absorption ranges.

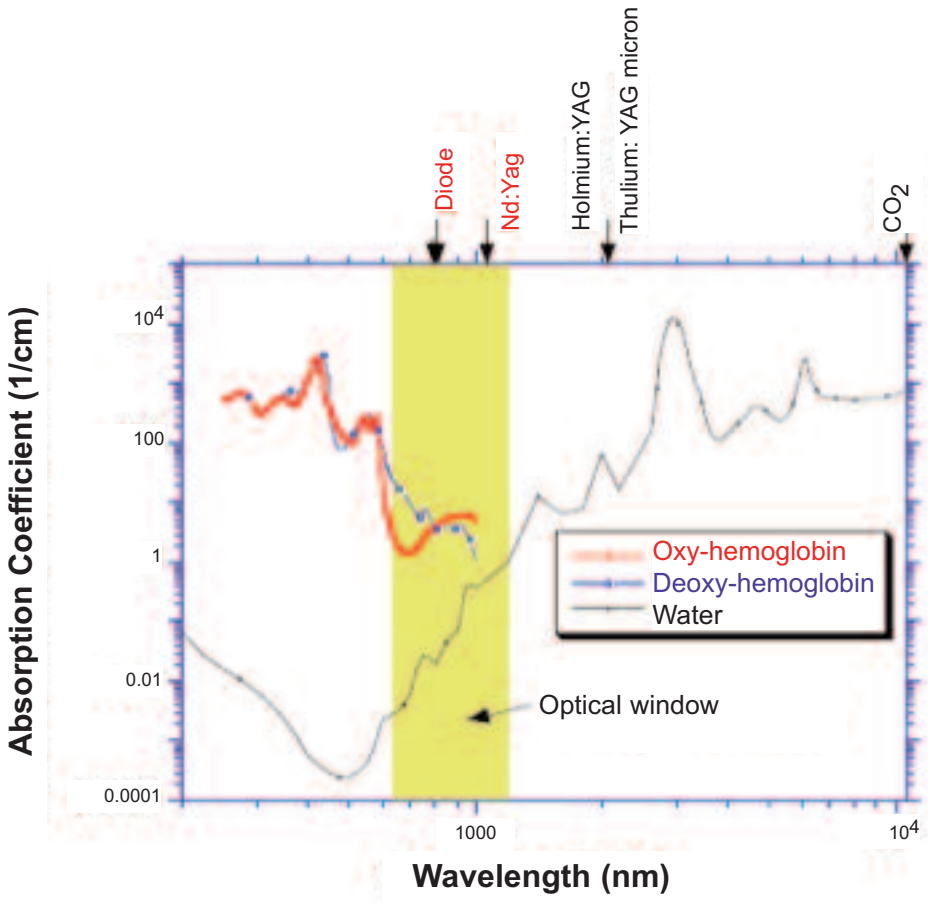


Fig.3 Dominant absorption coefficients in vascular tissue. In the near Infrared up to 1200 nm, blood is the main absorber. Above 1200 nm water becomes the dominant absorber. Two spectral regions: 800-1100 nm, absorption by blood:1100 nm and up absorption by water

In a separate study[10], we compare the different phases of action (Figure 1) of EVLA for various laser sources (ND-YAG 1064, Diode 810 nm, Holmium YAG 2µm en Thulium YAG cw 2µm) using a comparable experimental setup as described in Chapter 1. We observe that coagulum formation in blood was strongest for Diode and Thulium lasers, and coagulum formation is not present with Holmium laser. (Table1) With regard to temperature rise, we observe higher peak and mean temperature for Diode laser. Furthermore, we observe that the Thulium laser is in favour for long exposure to moderate temperature increase.

	Diode	Nd:YAG	Thulium	Holmium
Coagulation	++	+	++	-
Vaporization	++	+	++	-
High peak temperature	++	+	+	-
Average Temperature	+	+	+	+

Table 1 Comparison of phases in the mechanism of action in an experimental setup using different laser sources.

Figure 4 gives an estimation of the efficiency of laser light- to - heat transfer to the blood/vessel for the laser sources compared. The 2 µm thulium laser is the most effective in heating the environment per unit of time. Although the cw 2 µm laser has promising characteristics to perform EVLA, there are no clinical studies published yet. From our observations, this laser could be use in combination with a water flush during exposure to obtain a controlled heating inside the lumen.

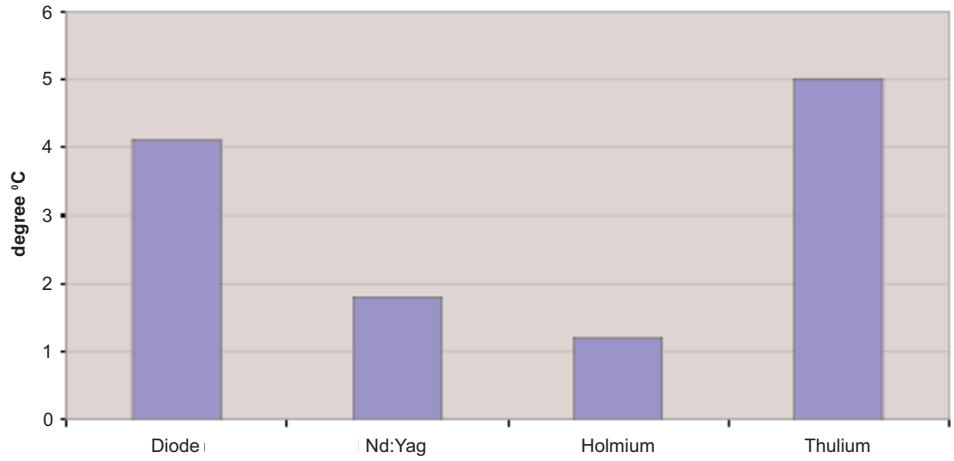


Fig. 4 The effectiveness of laser energy to heat transfer in the vessel is represented by the relative temperature rise per unit of time for various potential laser sources for EVLA.

There is no evidence in the literature to suggest that one laser wavelength/technique is more effective than the other[11]. Despite the use of various laser wavelengths and techniques of application (intermittent exposure and pulling speed) the results in literature only seem to be dependent on the total energy used per unit of length (J/cm)[12]. This observation attributes to the basic mechanism of action as we propose in this thesis: the formation of a coagulum that effectively converts laser energy to heat and steam independent of the wavelength clinically used (810, 980 and 1430 nm).

Large single-centre studies of EVLA using different wavelengths have reported early occlusion rates achieved of 97% to 98% with sustained occlusion being observed in more than 90 % of limbs at 3 years[13-17]. Two comparative studies[18, 19] demonstrate that patients treated with longer laser wavelengths report less postoperative pain and ecchymosis. Longer wavelengths have been hypothesized to penetrate deeper into the vein wall and studies in the porcine great saphenous vein demonstrate full thickness thermal damage at 5 W with the 1320 nm laser and at 20 W with the 1064 nm laser. Goldman et al[19] found a 1320-nm continuous laser with automatic catheter withdrawal to be better suited for saphenous vein obliteration than other laser wavelengths: 100 % occlusion at 6 and 12 month and no episodes of postoperative pain or thrombophlebitis as is also described by Weiss et al[9]. The safety of this laser wavelength is thought to be due to the lack of absorption of 1320 nm laser energy by haemoglobin. Chang[18] reports on the outcome of endovenous laser photocoagulation after high ligation of the GSV using very high rates of energy delivered from a Nd: YAG 1064 laser, with a 600 µ optical fibre. Laser power is set at 10 or 15W, delivered with pulse duration of 10 seconds and a withdrawal rate of 0.1 cm/s resulting in a mean laser dose of 15J /cm. After a mean follow-up of 19 months, 96.8% of the patients demonstrate a remarkable improvement, but the mean operative time is 82 (range 65-100) minutes and the complications rate is high, with an incidence of paraesthesia of 36.5% and an incidence of superficial skin burns of 4.8%. This can be explained by our observations that the Nd:YAG has a high penetration through blood and can induce deep thermal effects through and beyond the vein wall. During exposure in blood, the typical coagulum formation is strongly delayed or not formed at all. Thus, multiple laser wavelengths are suitable for endovenous ablation of the GSV. Whether 810-940 or 1470 nm is better suited for EVLA has to be studied in experimental settings and clinically evaluated in randomized controlled trials in larger populations with longer follow-up.

Mode of laser delivery: intermittent or continuous delivery

The choice of intermittent laser delivery for EVLA is primarily based on the description of the technique and the results reported by Min et al. in 2001[20]. With intermittent laser mode, the vein is exposed to fixed amounts of energy at equal distances. The total amount of energy delivered depends on the distance between the pulses, pulse duration and laser power. During continuous exposure the laser is pulled back more constantly and the total energy delivered depends on the pullback rate and the laser power. Intermittent laser energy has been shown to cause perforation of the vein with subsequently post procedural bleeding, whereas continuous laser energy is less disruptive of the vein wall[9]. This can easily be explained since in intermittent mode the fibre tip is fixed and potential in contact with the vessel wall during laser exposure while in continuous mode the fibre is constantly moving and does not remain at the same location during exposure. Side effects such as post procedural bruising may either be related to the administration of tumescent anaesthesia, to perforation caused by laser energy, or from direct contact between laser tip and vein wall. It can be expected that the fibre will be slightly bended and will have a super-

ficial contact with the vessel wall instead of a central position inside the lumen freely surrounded by blood. This explains the frequent observation of local perforations. The coagulum formed at the tip might actually prevent perforations. However, during retraction of the fibre, the coat of coagulum could come off and the direct exposure of the vessel wall with the fibre tip could result in a perforation before a new coating is formed. In Chapter 8 we presented the results of a study of the early pathological changes in non-varicose segments of the GSV from below the knee. We found that vein perforation with subsequent per vascular bleeding is seen in a few cases treated with 40-80 J/cm, and in all cases treated with 110-200 J/cm regardless of the mode of energy delivery. These results have been confirmed by others [7,9,21]. So, it seems, that post procedural bleeding, which does not seem to affect patient recovery, is related to the amount of energy delivered rather than to the mode of energy delivered. There is no evidence in the literature to suggest that one technique is more effective than the other. Although the fact that differences between intermittent and continuous delivery of exposure of laser light during EVLA are of interest, both schedules are in successfully daily use in clinical practice.

Amount of energy delivered.
The amount of energy delivered during EVLA is an important parameter in achieving complete occlusion of the GSV. The total energy delivered, expressed as Joules /cm, and equals the product of power (watts) and the pullback velocity of the catheter (cm/s). The study is performed in the early period of endovenous laser ablation using 40- 60 J/cm. However, the procedure for continuous withdrawal of the fibre using 14 W laser power and a pullback rate of 0.2 cm/s, delivering 70J/cm, has been adopted following confirmation that it does not carry an increased risk of lower GSV occlusion rates or adverse effects such as thrombophlebitis, pain and ecchymosis. In a multivariate study, Proebstle et al[14,15] demonstrates that that the amount of energy delivered is an independent predictor of GSV occlusion and confirms this in two randomized clinical trials showing that 60J/cm is more effective than 25 J/cm, and that 60J/cm or more was associated with durable results at 1- year follow-up. Timperman et al[16] suggests that more than 80 J/cm results in a success rate of 100%. In a mathematical model Mordon et al[22] suggests that 65 and 100J/cm is needed to destroy the intima of varicose veins with a diameter of 3 and 5 mm. A recent prospective study reports that a higher dose of laser energy (30 W compared to 15W) shows an immediate success rate of 100% and a significantly reduced recanalization rate during a 12 month follow-up (97% versus 82.7%)[23]. Generally, a range from 60 to 80 J/cm is safe and affective in GSV ablation.

Diameter of the vessel.
Vein diameter, tumescent anaesthesia and the amount of energy are the most important factors in order to achieve a procedure without complications, a permanent occlusion and absence or a very low rate of recanalization in the follow-up. Theoretically, the optical fibre should be placed at the centre of the vein lumen in order to have a homogenous distribution of energy around the vein wall and produ-

ce a symmetrical damage. Considering the extreme variability of the vein diameter along the treated vein length or between different patients and also the morphological variability of the diseased vein walls, the only way to standardize there is by producing a vein spasm that will make the vein to encircle the catheter. However, as we have shown in our in vitro study and supported by observation in vivo, steam bubbles are formed that homogeneously filled the lumen of the vessel suggesting the position of the fibre tip is less critical then theoretically assumed. Larger GSV diameters are associated with early treatment failure[16]. Mathematical modelling of EVLA provides a better understanding of the ablating process and may determine the optimal dosage as a function of vein diameter. To illustrate this dependence, in figure 5 the results are shown of a simple calculation of the theoretical temperature rise in relation tot the diameter of the vein not taking phase changes into account.

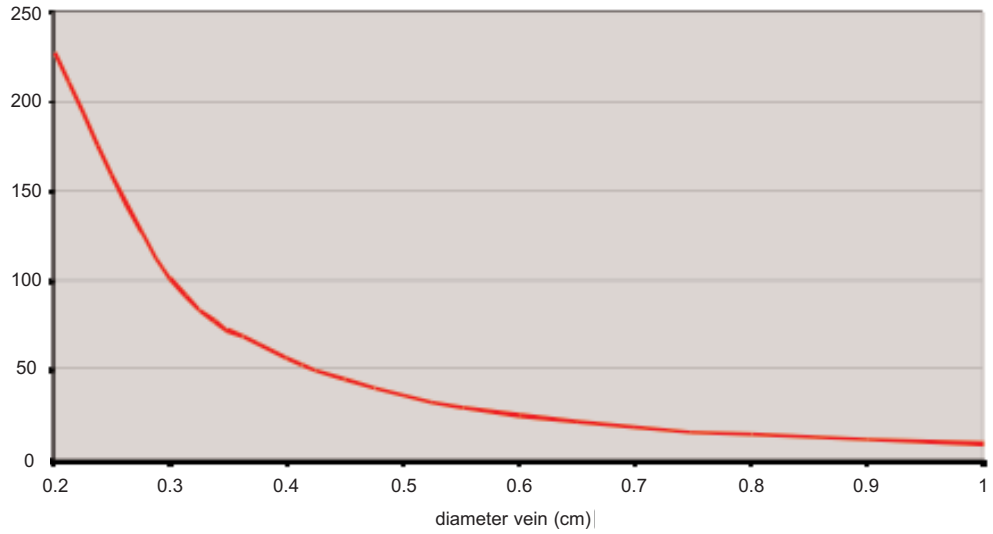


Fig. 5 Temperature rise in relation to the diameter of the vein applying an exposure of 30 J/cm calculated in a simple model without phase changes.

Also the deformation of the vein by external pressure can have a major impact on the temperature rise in the vein as illustrated by our calculations in a simplified vein model (Figure 6).

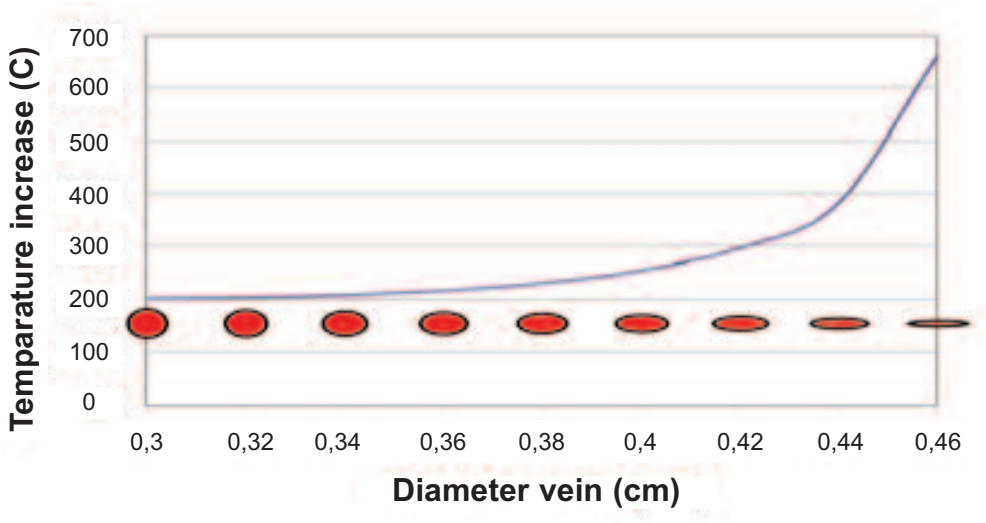


Figure 6: Relative temperature rise in relation to the diameter of the vein which increases when deformed by external force.

Other authors like Mordon[14] have performed calculation in vein models and reports results that in a pulsed mode for 3 mm vein diameter a minimum of 15 J/cm are required to obtain a permanent damage. For a 5 mm vein diameter 50 J/cm is required. Recently, Kontothanassis[24] suggests, in order achieving a high rate of success without adverse effects, to infuse high volume of cold tumescent saline (400-500 ml) associates with local anaesthetic agents, to completely collapse the vein. Once the vein encircles the catheter the amount of energy to deliver is calculated as: 9 X mm of vein diameter before tumescent anaesthesia x cm of incompetent vein. Immediate results are excellent: 100 % occlusion and no adverse effects.

Temperature during EVLA

We record large variations of intravenous temperatures during EVLA. Three mm away from the centre of the thermography catheter, we measure minimal temperatures rise and temperatures up to 300 ^{0}C. Very local temperatures at the fibre tip exceeding 1000 ^{0}C (bright light flashes of carbon vaporization) have been described previously. Weiss[7] measures the temperature in goat veins. The highest average temperature (719 ^{0}C) is recorded at the laser tip, and temperatures of 307 ^{0}C and 231 ^{0}C are recorded 2 mm distal and 2 mm proximal to the tip. These high temperatures must be attributed to the hot vapour environment within the insulating coagulum coating. Zimmet and Min [18] measures temperature at the outer vein wall in a

pig ear and conclude that peak temperatures lower than 50 °C are unlikely to cause permanent damage to perivenous tissues. Beale et al[25] measures temperature in 12 patients undergoing EVLA. The maximum recorded temperature 3, 5, and 10 mm from the GSV is 43.3°C, 42.0°C, and 36.0°C. The peak temperature is lower if perivenous infiltration is used6. So, despite the high localized temperatures generated during EVLA, published data suggest that transmission of heat into the surrounding tissue is minimal.

The role of blood during EVLA

The role of blood during EVLA must be considered. 810 nm diode lasers are used because the energy is absorbed by deoxygenated haemoglobin. The presence of too much blood reduces the light transmitted to the vein wall. Moreover, if the laser energy is entirely absorbed by blood, the initial success rate is mainly due to a thrombotic effect, but thrombus dissolution leads to recanalization. Thus, reducing the amount of blood in the vein is recommended by emptying the vein lumen by means of raising the leg in Trendelenburg position, the use of perivenous infiltration with tumescent saline solution, and manual compression over the GSV during the procedure. However, there will still be blood present in the lumen sufficient (e.g. inflow from side branches) to initiate the formation of the coagulum, as already shown before, and consequently steam formation filling the lumen of the vein. The volume of blood displaced will contribute to more energy available to heat the vessel wall. In our other studies we showed that the coagulum is also formed in 50% diluted blood and active saline flushing along the catheter tip during exposure will suppress the formation of the coagulum[26].

Which factors influence the safety of endovenous laser treatment?

With regard to perivascular damage after EVLA, we perform two studies described in Chapter 7 and 8. **In chapter 7**, we present the results of a prospective analysis of the influence of EVLA on the function of lymph vessels in the leg, because lymph vessels run alongside the GSV in the leg. Of 120 patients in a clinical trial comparing cryostripping and EVLA, 33 agree to participate in the study. Patients underwent lymphoscintigraphy before and 6 months after EVLA or cryostripping. Six months after treatment, none of the 17 patients treated with EVLA and 1 (6.3%) of the 16 patients treated with cryostripping have clinical grade 1 lymphoedema, with marked disruption of the lymphatics around the knee being visible on scintigrams. This patient also shows an abnormal uptake of radioactive tracer at the groin, 120 minutes after injection. In **Chapter 8**, we describe the early pathological changes in the non-varicose GSV below the knee and investigated possible saphenous nerve damage after EVLA. We found many saphenous nerve fibers and its side branches adjacent to the veins but in none of the slides damage of the nerves or perineural structures is observed. No vein thrombosis or hemolysis of vasa nervosum is noted in any of the specimens. Although, the number of patients in these two studies is too small to allow firm conclusion to be drawn, the preliminary experience with EVLA shows that there is minimal damage to the lymphatic system and minimal risk of

saphenous nerve damage. The incidence of saphenous nerve paraesthesia has been reported to range from 1% to 36.5%[17]. Fortunately, in most cases the damage is self limiting and often resolves within 6-8 weeks of the procedure. Proper administration of sufficient tumescent anaesthesia within the fascia surrounding the GSV increases the distance between the vein and the saphenous nerve, thereby reducing the risk of nerve damage. Pain, ecchymosis, and superficial thrombophlebitis are commonly mentioned minor adverse effects of EVLA, but in most cases they are self-limiting and disappear in 1-2 weeks. They can be reduced by elastic stockings and medication. Although endovenous laser techniques do not have classical surgical side effects such as wound infection and scarring they may be associated with specific laser induced adverse effects such are skin burns and deep vein thrombosis. Skin burns are a potential complication of EVLA but the reported incidence is low and most of the skin burns are superficial. Skin burns may occur if the amount of energy delivered is too high or if the cooling effect of tumescent anaesthesia is insufficient. Cutaneous skin burns can be best prevented by generous use of infiltrating tumescent anaesthesia along the entire length of the GSV. Additionally, care should be taken to give attention to when the laser approaches the puncture site. In EVLA, deep vein thrombosis is often described as an extension of the thrombus from the SFJ into the common femoral vein. Unlike surgical stripping of the GSV, EVLA does not allow for flush occlusion of the GSV. The potential for thrombus extension is therefore real because most techniques recommend leaving the proximal 1cm of the GSV open to maintain the patency of the SFJ and inferior epigastric vein. Despite these concerns, the incidence of thrombus extension info the common femoral vein or deep vein thrombosis is only 0.3 % after EVLA[27]. The incidence is sufficiently low that the consensus of opinions remains against routine GSV ligation. The role of pharmacological prophylaxis remains uncertain but we emphasize the importance of early mobilization and the use of compression stockings for patients who undergo EVLA. Subcutaneous heparin should be used in high risk patients because these patients will benefit from thrombosis prophylaxis.

2. Clinical studies

Chapter 3 presents the results of a 2- year study of the first 100 EVLA procedures in 85 patients. We find that not all patients with GSV reflux are suitable candidates for this procedure. For example, those with a very large and tortuous GSV or a history of thrombophlebitis are not suitable for EVLA because it is not possible to introduce or pass the guide wire or sheath through their veins. Furthermore, performing EVLA requires experience and skill. All technical failures (7.5%) and 73% (n=11) of the treatment failures occurred in the first half of the studied population, indicating the learning curve effect. The technical failure rate can be explained by the fact that the method was new and the surgeon was at the beginning of the learning curve. Common problems are difficulty gaining access to the vein, a mismatch between sheath length and the length of the treated GSV and inadequate delivery of anaesthesia into the fascial sheath of the GSV. Mean energy delivered per unit length was 39 ± 8 J/cm (range 25-65) for successful treatment (n=78) and 30 ± 10 J/cm (range 21-50) for failed treatment (n=15). Our results, with 84% anatomical success and 89% functional success with complications such as bruising (31%), tightness (17%), pain (14%), induration (2%), and thrombophlebitis (2%), are comparable with those of other studies, but not outstanding.

We find EVLA to be effective in causing occlusion of the GSV. The use of tumescent local anaesthesia, manual compression over the vein during the procedure, and a fibre tip position 0.5–1 cm below the SFJ are important technical aspects of the procedure and make it possible to treat veins of any diameter with EVLA. GSV occlusion and early recanalization are related to the amount of laser energy delivered[13, 14]. Proebstle et al[23] compares 15 W of energy delivered with a 5 mm/s pull back time with 30 W of energy delivered with a 3 to 4 mm/s pullback time in the treatment of 263 limbs and find complete occlusion rates at 12 month of 82.7% and 97.7% for the procedures, respectively. Differences are attributed to more vigorous steam bubble formation with 30 W of energy with a greater transfer of heat to the endothelium. Timperman et al [16] treats 111 limbs with a mean energy delivered of 58.7 ± 24.4 J/cm. The energy delivered is 63.3 ±.26.6 in successfully treated veins and averaged 46.6 ± 13.8 J/cm in veins that remained patent. A prospective study determines that energy levels greater than 80 J/cm are associated with a success rate of 95%. Nowadays, we use a power setting of 14 W and a pullback rate of 0.2 cm/s, delivering 70 J/ cm. Generally, a range of 60 to 80 J-cm is safe and results in effective ablation.

In **chapter 4** we present the results of a randomized clinical trial obtained 2 years after EVLA with and without ligation of the saphenofemoral junction (SFJ) in 43 patients with bilateral varicose veins. We hypothesize that additional SFJ ligation will not improve the outcome of EVLA 2 years after treatment. Patients received bilateral treatment in which one limb receives EVLA without SFJ ligation, whereas the

other limb receives EVLA with SFJ ligation. Thirty-eight (88.4%) treated GSV segments are ablated completely in the EVLA without ligation group and 42 (97.7%) in the EVLA with ligation group (P=0.2020). In the EVLA without ligation group, 4 limbs (9.3%) have type 1a varicose vein recurrence, 3 (7.0%) limbs have type 1B varicose veins recurrence (anterior saphenous vein n = 3), and no limbs have type 1C varicose veins. In the EVLA with ligation group, no limbs have type 1a or 1B and 5 limbs (11.6%) have type 1C. Two-year life table analysis shows freedom from groin varicose vein recurrence in 83.3% of limbs (95% CI; 67.2–94.7) treated with EVLA without ligation and in 87.4% (95%; CI 72.6–96.7) of limbs treated with EVLA with ligation group (P=0.4654).

To perform EVLA of the GSV without crossectomie breaks a fundamental rule of venous surgery, which establishes that each SFJ tributaries should be ligated separately. Moreover, the absence of high ligation could enable clot diffusion to the femoral vein[27]. The success of EVLA has been shown to be dependent upon the amount of energy delivered, with non-occlusion and reopening of the GSV occurring more frequently if an energy level less than 70 J/cm is delivered[14-16]. We found that the GSV reopened in 7.3% of limbs after EVLA without ligation, which is in accordance with the published data of 0-10.8%[14,15,17]. In these failed procedures we delivered less than 70 J/cm. However, as stated by other authors [12, 13, 16, 23] successful GSV ablation depends not only on the mode and amount of laser energy delivered, laser wavelength, and pullback rate, but also on methodological aspects, such as the use of perivenous infiltration, manual compression over the vein during the procedure, and a fibre tip position 0.5–1 cm below the SFJ. Incompetent tributaries at the SFJ are detected in 6 (3.7%) of 163 SFJ tributaries visible on duplex scanning at baseline. These require additional therapy at 6 weeks to achieve a successful clinical outcome. In the EVLA without ligation group, 3 (7.7%) of 39 limbs develops duplex proven groin recurrence due to incompetent tributaries and none in the EVLA with ligation at the 2 year follow-up Thus, leaving non refluxing tributaries at the SFJ does not appear to have an adverse impact on clinical outcome[12]. Reflux into an untreated tributary is possible and could lead to recurrent varicose veins; however, the exact incidence is not known but appears to be low. Groin recurrence due to neovascularization is observed in 5 limbs after EVLA with ligation and none in EVLA without ligation. The absence of neovascularization in the EVLA without ligation group may be explained by the closed technique used, which does not result in groin haematoma or angiogenesis[28, 29]. Chandler et al[30] have suggested that avoiding surgical disruption of the SFJ may reduce neovascularization and thus recurrence rates may be lower. Recent studies [23,31], have shown that SFJ ligation may be of little advantage after effective endovenous procedures and that neovascularization is more frequent than after surgical treatment. Thus, there is no difference in SFJ ligation to EVLA in the short term outcome. Whether SFJ ligation results in a poorer long-term outcome has to be studied in larger populations with longer follow-up.

In **chapter 5** we present the 2-year results of a randomized clinical trial of EVLA compared with cryostripping in 120 patients with varicose veins of the GSV. We hypothesize, that there would be a 15% difference in freedom from recurrence, to the prejudice of the EVLA group. In the EVLA group, the GSV segment is ablated completely in 57 (95.0%) patients. In the cryostripping group, the flexible tip probe is successfully introduced in the GSV below the knee and the GSV is stripped completely in 60 (100%) patients. EVLA provides significantly more favourable results than cryostripping with regard to operative time, post-procedural pain, induration, activity impairment, and patient satisfaction, and not significantly with regard to complications and freedom from recurrence. Two-year life table analysis shows overall freedom from varicose veins recurrence in 77.4% of patients (95% CI; 71.7–78.0) in the EVLA group and in 66.0% of patients (95% CI 60.0-67.4) in the cryostripping group (P=0.2531). Scores for venous clinical severity and Aberdeen Varicose Vein Severity are improved significantly after treatment but the difference between the groups is not significant.

To our knowledge, this is the first single-centre study comparing EVLA and cryostripping in a randomized controlled trial with a follow-up of 2 years, a refusal rate of 10.4%, and a lost to follow-up rate of 7.5%. Until now, only two randomized controlled trials comparing EVLA and surgical stripping have been published. Rasmussen et al[32] reports that the short term efficacy and safety of EVLA and surgical stripping are comparable, except for slightly increased pain and bruising in the surgical stripping group, and that the treatments are equally effective in improving venous clinical severity scores, Aberdeen Varicose Vein Severity score, and Short-Form 36. The randomized trial recently reports by Darwood[33] et al describes similar short-term results with no important outcome difference between surgery and endovenous laser. Minor complications are not infrequent (12.2%) after surgery with wound infection (5.3%) being the most common. Sensory disturbances are also frequently reported (16-52%) after surgery. Sensory disturbances and skin burns are seldom reported after 810 nm EVLA. The results of the present study and the reported results of randomized and non-randomized trial has show that there are significant improvements in both generic and disease-specific quality of life after both procedures, but that there is a significant deterioration of quality of life in the early post-operative recovery period after surgery. With regard to recurrence rates following treatment, the reported 2-year recurrence rates after surgery vary between 13 % and 40%[2,13]. The recurrence rates following EVLA vary between 3% and 10% but longer follow-up in randomized clinical trials is necessary to establish the real recurrence rate. Neovascularization, not inadequate surgery, is the most common cause of recurrence after surgery, as we also observe. Neovascularization seems to be stimulated by angiogenic factors associated with surgical dissection, wound healing, and tissue repair[29, 30]. These factors are likely to be reduced with endovenous procedures such as EVLA and radiofrequency (RFA) which might explain the lower rate of groin recurrence rate with these procedures. So, it seems that both EVLA and cryostripping are effective in patients with varicose veins, but that patients favour EVLA

because of its better cosmetic results, lower rates of postoperative morbidity, lower rates of activity impairment, and lower recurrence rates up to 2 years.

In **chapter 6** we present the 2-year results of a randomized comparison of costs and cost-effectiveness of cryostripping versus EVLA for varicose veins. Data from a randomized controlled trial comparing cryostripping and EVLA in 120 patients are combined to study Short-Form (SF) 6D outcome, costs, and cost-effectiveness 2 years after treatment. Incremental cost per quality adjusted life year (QALY) gained 2 years after treatment is calculated using different strategies and uncertainty is assessed with bootstrapping. Two year after treatment, QALY (SF-6D) is 1.59 (95% CI, 1.53-1.64) in patients who underwent cryostripping and 1.60 (95% CI 1.55-1.64) in patients who underwent EVLA. Cryostripping cost € 2651 per patient (95 % CI 2501-2820) and EVLA € 2783 (95% CI 2638-2937). Bootstrapping indicated that cryostripping is associated with an incremental cost-effectiveness ratio of € 32 (95 % CI -240-173) per QALY gained. With regard to different strategies, outpatient cryostripping appeared the dominant strategy, i.e. is less costly and more effective 2 years after treatment. When we compared outpatient cryostripping with outpatient EVLA and 50 % lower costs of the EVLA kit, the cost-effectiveness ratio (€/QALY) was 1623 (95% CI 1317-1920) for cryostripping and 1681 (95% CI 1547-1744) for outpatient EVLA, only a limited difference remaining of 46 €/QALY.

In this cost comparison, the cost of the laser apparatus, fibre kit, and the Duplex ultrasound are major factors that increases the costs of EVLA group. In contrast, hospital stay and anaesthesia (conduction or general) are important factors that increase the cost of cryostripping. Day-care procedures significantly increase the cost of both interventions. The cost of lost productivity significantly increases the costs of cryostripping, but there was no significant difference in the proportion and costs of additional procedures performed 6 weeks after treatment and during the follow-up period. Ratcliffe et al[34] publishes the results of a randomized clinical trial of surgery versus conservative treatment and concludes that for patients with uncomplicated varicose veins and evidence of saphenofemoral reflux surgical treatment offers a modest health benefit for relatively little additional costs. Rautio et al[35] compares endovenous obliteration (Closure System, VNUS Medical Technologies Inc, Sunnyvale, California) and surgical stripping in a randomized controlled trial and found that endovenous obliteration is cost-saving for society, especially among employed patients. Recently, however, Rasmussen et al[32] reported short term results of a randomized controlled trial comparing ELA and surgical stripping and calculates that the mean costs of surgical stripping is lower, when loss of productivity is included (€ 3084 versus € 3396).

3. Future perspectives.

Are there other techniques that can replace surgery in the near future? The idea of using endovenous electrosurgical devices to denature the collagen in the vein wall is not new and monopolar electrosurgical desiccation has been used. In 2000, Manfrini and Chandler[36] reported on endovenous obliteration with radiofrequency resistive heating (RFA) as a more advanced method, including precise heating with feedback controlled by the vein wall temperature and impedance. Radiofrequency is electromagnetic radiation in the frequency range 3 KHz to 300 GHz. A commercially available radiofrequency generator produces waveforms and supplies radiofrequency energy to the catheter electrodes, which induces irreversible denaturation of collagen, transforming the native helical of collagen into a more random, coiled structure. Denaturation results in the irreversible shrinkage of collagen which is thereby a convenient measure thermal damage. Experimental studies have shown that collagen tissue can be shortened precisely by applying heat. The effectiveness of RFA depends on carefully controlled heating up to a temperature sufficient to denature collagen in the venous wall to an extent that will cause maximal lumen contraction without destroying the integrity of the vein. While laser energy is delivered endovenously from the laser fibre tip and is highly focused, with laser tip temperatures > 300 ^{0}C, RFA operates with resistive heating of the vein wall in its whole circumference, generating temperatures of 85^{0} to 90 ^{0}C. As a result, EVLA is generally associated with vein wall perforation and this is one of the reasons why EVLA is associated with a higher rate of bruising. However, the mode of action of RFA results in a significantly prolonged ablation time compared with that of EVLA (2-3 cm/min for RFA and 10-20 cm/min for EVLA) and is one of the reasons why RFA is associated with a higher rate of deep vein thrombosis and potential nerve damage due to due to thermal conduction to a larger distance from the vessel. A second drawback is the higher cost of disposable catheters compared with the EVLA laser fibre kit. Recently, a new radiofrequency powered catheter (VNUS® ClosureFast) based on the principle of segmental thermal ablation has developed using higher catheter feed back speed and stable temperatures of 120 ^{0}C[37].

Duplex guided foam sclerotherapy. Sclerotherapy using liquid sclerosant is effective for the treatment of small varicose veins. However, the application of ultrasound guidance to sclerotherapy has led to improvements in this technique. Varisolve® polidocanol microfoam is new microfoam that was developed to provide several advantages over conventional foams, including consistent microfoam quality, bubble size and sterility. Varisolve polidocanol is uniform foam of physiological gases, principally oxygen and carbon dioxide combined with 1% aqueous solution of polidocanol[38].

With regard to the “best treatment for varicose veins” there are several treatment modalities available for varicose veins including foam sclerotherapy, thermal ablation and open surgery. Sclerotherapy is non-invasive, requires local anaesthetic, has a short recovery time and does not have high start up or supply costs. But, as a single modality, limitations do exist, the most frequently mentioned being that the current treatment for larger bulging varicose veins is only 50-60% effective 2 years

after treatment.[39] The benefits of open surgery are well documented; it is a well-studied procedure, having been performed for over a century, it is easy to teach, and it is less expensive than new procedures. In contrast, thermal ablation procedures have only been used for 10 years and there are few studies documenting their long term effect. Moreover, these procedures require more specialized training and the costly devices keep procedure costs high. The limited medical literature available for newer procedures also makes it difficult to compare recurrence rates. Randomized controlled trials with adequate follow-up comparing new techniques are needed.
More specifically:

1. The value of endovenous laser treatment using different wavelengths (810 nm and 1470 nm and potentially the Holmium laser) needs further evaluation and requires comparison with radiofrequency using VNUS® ClosureFast.
2. The value of endovenous laser treatment in patients with small saphenous varicose veins need further evaluation and requires comparison with small saphenous vein stripping and with Duplex guided foam sclerotherapy.
3. The value of endovenous laser treatment for patients with C2, Ep, AS2, Pr venous disease needs further evaluation and comparison with Duplex guided foam sclerotherapy.
4. The values of endovenous laser treatment from ankle to groin for patients with C2, Ep, AS3, Pr venous disease needs further evaluation and comparison with radiofrequency using VNUS® ClosureFast.

4. Conclusions.

This study has shown clear advantages of endovenous laser treatment and cryostripping of varicose veins across a whole range of outcome measures relating to health status, quality of life and patient satisfaction. But from a patient's prospective, EVLA is preferred to cryostripping because of its better cosmetic results, lower rates of postoperative morbidity, and lower rates of activity impairment. From a doctor's prospective EVLA is preferred to cryostripping because of its shorter operative time, lower rates of complications, and lower recurrence rates up to 2 years. From a health service perspective, EVLA is preferred to cryostripping because the procedure can be performed in an outpatient setting using local anaesthesia, and is associated with greater patient satisfaction and lower costs of lost productivity

Main conclusions of this thesis

1. Application of endovenous laser causes heterogeneously heating of the vessel wall by intraluminal expanding steam bubbles created from a coagulum of blood around the laser fibre tip (Objective 1).
2. EVLA is a feasible, safe and fast procedure for eliminating GSV reflux and provides excellent cosmetic results and patient satisfaction (Objective 2).
3. Short-tern outcome is not different if EVLA is performed with or without SFJ ligation. Adjunct SFJ ligation tends to be associated with a poorer long-term outcome due to neovascularization (Objective 3).

4. Both EVLA and cryostripping are effective in patients with varicose veins, but patients favour EVLA because of its better cosmetic results, lower rates of post-operative morbidity, lower rates of activity impairment, and lower recurrence rates up to 2 years (Objective 4).
5. In terms of costs per QALY (SF-6D) gained outpatient cryostripping appears to be the dominant strategy, but EVLA provides comparable outcomes for a relatively little additional costs (Objective 5).
6. Whether endovenous laser treatment can reduce lymphatic damage has to be awaited. Preliminary experience with EVLA suggest that lymphatic damage might be minimal (Objective 6).
7. Whether endovenous laser ablation of the GSV below the knee is safe and effective has yet to be established. Preliminary experience with EVLA shows that the risk of saphenous nerve damage might be minimal (Objective 7).

References:

1. Brand FN, Dannenberg AC, Abbott R D et al. The epidemiology of varicose veins: the Framingham study Am J Prev Med 1988; 4:960-1001.
2. Labropoulos N, Leon M, Nicolaides AN, Giannoukas AD, Volteas N, Chan P. Superficial venous insufficiency: correlation of anatomic extent of reflux with clinical symptoms and signs. J Vasc Surg 1994:20:953-958.
3. Dwerryhouse S, Davies B, Harradine K, Earnshaw JJ. Stripping of the long saphenous vein reduces the rate of reoperation for recurrent varicose veins: five year results of a randomized trial. J Vas Surg 1999;29(4):589-592.
4. Winterborn RJ, Foy C, Earnshaw JJ. Causes of varicose vein recurrence: late results of a randomized controlled clinical trial of stripping the long saphenous vein. J Vasc Surg 2004; 40(4):634-639.
5. Rutgers PH, Kitselaar PJEHM. Randomized trial of stripping versus high ligation combined with sclerotherapy in the treatment of the incompetent greater saphenous vein Am J Surg. 1994:168:311-315.
6. Boné C. Tratamiento endoluminal de las varices con laser de diode: estudio prelimary. Rev Patol Vasc 1999; 5:35-46.
7. Corcos L Dini |S, de Anna D et al. The immediate effects of endovenous diode 808 nm laser in the greater saphenous vein: morphologic study and clinical implications J Vas Surg 2004; 30:174-178.
8. Proebstle TM, Sandhofer M, Kargl A, Gul D, Rother W, Knop J et al. Thermal damage of the inner vein wall during endovenous laser treatment: key role of energy absorption by intravascular blood. Dermatol Surg 2002; 28(7):596-600.
9. Weiss RA. Comparison of endovenous radiofrequency versus 810 nm diode occlusion of large veins in animal model. Dermatol Surg 2002; 28(1):56-61.
10. Rem AI. van Thoor S, Verdaasdonk RM, Disselhoff BC, der Kinderen DJ. Mechanism of Endovenous Laser Treatment revealed using temperature and imaging strategies comparing Diode, Nd:YAG, Thulium and Holmium laser systems . Abstract supplement, Lasers in Surgery and Medicine, April 2006).

11. Kabnick LS. Outcome of different endovenous laser wavelengths for great saphenous vein ablation. J Vasc Surg 2006; 43:88-93.
12. Theivacumar NS, Dellagrammaticas D, Beale RJ, Mavor AI et al. Fate and clinical significance of saphenofemoral junction tributaries following endovenous laser ablation of great saphenous vein. Br J Surg 2007; 94: 722-725.
13. Min RJ, Khilnani N, Zimmet SE. Endovenous laser treatment of saphenous vein reflux: long term results. J Vasc Interv Radiol. 2003; 14: 991-996.
14. Proebstle TM, Gul D, Lehr HA, Karg lA, Knop J. infrequent early recanalization of greater saphenous vein after endovenous laser treatment. J Vasc Surg 2003; 38(3):511-516.
15. Proebstle TM, Krummenauer F, Gul D, Knop J. Nonocclusion and early reopening of the great saphenous vein after endovenous laser treatment is fluence dependent. Dermatol Surg, 2004; 30(2): 174-178.
16. Timperman PE, Sichlau M, and Ryu RK. Greater energy delivery improves treatment success of endovenous laser treatment of incompetent saphenous veins. J Vasc Interv. Radiol 2004; 15: 1061-1063.
17. Mundy L, Merlin TL, Fitridge RA, Hiller JE. Systematic review of endovenous laser treatment for varicose veins. BJS 2005; 92:1189-1194.
18. Chang C, Chua J. Endovascular laser photocoagulation for varicose veins. Lasers Surg Med 2002; 32:257-262.
19. Goldman MP, Maurico M, Rao J. Intravascular 1320-nm Laser closure of the great saphenous vein: a 6-to12-month follow-up study. Dermatol Surg 2004; 30:1380-1385.
20. Min RJ, Zimmet SE, Isaacs MN, Forrestal MD. Endovenous laser treatment of the incompetent greater saphenous vein. J Vasc Interv Radiol 2001 Oct; 12(10): 1167-1171.
21. Zimmet SE, Min RJ. Changes in perivenous tissue during endovenous laser treatment in a swine model. J Vasc Interv Radiol 2003; 14:911-915.
22. Mordon SR, Wassmer B, Zemmouri J. Mathematical modelling of endovenous laser treatment. Biomed Eng Online 2006; 25:5-26.
23. Proebstle TM. Reduced recanalization rates of the great saphenous vein after endovenous laser treatment with increased energy dosing: definition of a threshold for the endovenous fluence equivalent. J Vasc Surg 2006; 44: 834-839.
24. Kontothanasis D, Di Mitri R, Ferrari Ruffino S, Labropoulos N. Endovenous thermal ablation. Standardization of laser energy: literature review and personal experience. Int Angiol 2007; 26:183-188.
25. Beale RJ, Mavor AIDF, Gough MJ. Heat dissipation during endovenous laser treatment of varicose veins: is there a risk of nerve damage. Phlebology 2006; 21(1):32-35.
26. Rem AI, Disselhoff BC, Klaessens J, Verdaasdonk RM. The influence of compressed vein shape and blood concentration on heat generation during endovenous laser treatment for varicose veins. Abstracts supplement April 2008, Laser in Surgery and Medicine.

27. Mozes G, Kalra M, Carmo M, Swenson L et al. Extension of saphenous thrombus into the femoral vein: A potential complication of new endovenous techniques. J Vasc Surg 2005; 41:130.
28. van Rij AM, Jones GT, Hill GB, Jiang P. Neovascularization and recurrent varicose veins: more histological and ultrasound evidence. J Vas Surg 2004; 40: 296-302.
29. Glass GM. Neovascularization in recurrence of the varicose great saphenous vein following transaction. Phlebology 1987;2:81-91.
30. Chandler JG, Pichot O, Sessa C et al. Defining the role of extended saphenofemoral junction ligation: a prospective comparative study. J Vasc Surg 2000; 32:941-953.
31. Kianifard B, Holdstok JM, Whiteley MS. Radiofrequency ablation (VNUS closure) does not cause neo-vascularisation at the groin at one year: results of a case controlled study. Surgeon 2006:4(2):71-74.
32. Rasmussen LH, Bjoern L, Lawaetz M, Bleming A et al. Randomized trial comparing endovenous laser ablation of the great saphenous with high ligation and stripping in patient with varicose veins: short-term results. J Vasc Surg 2007; 46:308-315.
33. Darwoord RJ, Theivacumar N, Dellagrammaticas D, Mavor AI et al. Randomized clinical trial comparing endovenous laser ablation with surgery for the treatment of primary great saphenous varicose veins. Br J Surg 2008 Mar; 95(3):294-301.
34. Ratcliffe J, Brazier JE, Campbell WB, Palfreyman S, MacIntyre JB et al. Cost-effectiveness analysis of surgery versus conservative treatment for uncomplicated varicose veins in a randomized trial. Br J S 2006; 93:182-186.
35. Rautio T, Ohinmaa A. Perala J, Ohtonen P. Endovenous obliteration versus conventional stripping operation in the treatment of primary varicose veins: a randomized controlled trial with comparison of costs. J Vas Surg 2002; 35:958-65.
36. Manfrini S, Gasbarro V, Danielsson G, Norgen L, Chandler JG, Lennox AF et al. Endovenous management of saphenous vein reflux. J Vasc Surg 2000; 32(2):330-342.
37. Proebstle TM, Vago B, Alm J, Goeckeritz O et al. Treatment of the incompetent great saphenous vein by endovenous radiofrequency powered segmental ablation: First clinical experience. J Vasc Surg. 2008 Jan;47(1):151-156.
38. Wright D, Gobin JP, Bradburry AW, Coleridge Smith P, Spoelstra H et al. Varisolve® polidocanol microfoam compared with surgery or sclerotherapy in the management of varicose veins in the presence of trunk vein incompetence: European randomized controlled trial. Phlebology 2006; 21:180-90.
39. Beale RJ, Gough M. treatment options for primary varicose veins – A review. Eur J Vasc Endovasc 2005; 30:83-95.
40. Evans CJ Fowkes Fg, Ruckely Cv, Lee Aj. Prevalence of varicose veins and chronic venous insufficiency in men and women in the general population: Edinburgh Vein Study. J Epidemiol Comm Health 1999;53-149-153.

Chapter 10

Samenvatting

De meest toegepaste behandeling van varices: het strippen.
De meest toegepaste operatieve behandeling is crossectomie en het strippen van de vena saphena magna (VSM). Keller heeft de eer om ruim 100 jaar geleden de stripping operatie voor het eerst uit voeren (1905). Via een kleine snee in de lies wordt de verbinding van de VSM met de vena femoralis (de diepe ader) onderbroken en alle overige zijtakken worden onderbonden (de crossectomie). Via een tweede incisie even onder de knie wordt een geleider (stripper) in de VSM ingebracht en opgevoerd naar de lies en via de onderbonden VSM stomp weer naar buiten de ader gebracht. Het distale deel van de VSM wordt doorgenomen en de stripper wordt aan het uiteinde van de VSM bevestigd. Hierna wordt onder het aanleggen van een drukverband de VSM gestript. Het verwijderen van de VSM vanaf de enkel tot aan de lies (lange strippen) is verlaten wegens de grote kans (30%) op zenuwletsel aan het onderbeen terwijl de uitkomst van deze behandeling vergelijkbaar is met het strippen vanaf de lies tot even onder de knie. Het strippen vereist opname in een ziekenhuis, het gebruik van een operatiekamer, regionale of algehele verdoving, geeft een tweetal littekens en een aanzienlijke kans op bloeduitstortingen en wondcomplicaties. Hoewel de resultaten van deze behandeling op korte termijn goed zijn, is het recidiefpercentage op langere termijn aanzienlijk: na 5 jaar heeft bijna 40 % van de behandelde patiënten recidief varices. Naar schatting is 20 % van de varices operaties voor recidief varices. Sinds de introductie van cryostripping in 1982 wordt in plaats van de stripper een metalen probe met flexibele tip tot even voorbij de knie door de VSM opgevoerd, en de tip van de cryoprobe wordt vervolgens tot -850C bevroren. Hierdoor vriest de VSM vast aan de probe en de VSM kan daarna, zonder het maken van een tweede incisie, worden losgetrokken en verwijderd. Deze procedure heeft als voordeel dat er slechts een snee nodig is, de patiënt minder pijn ervaart, de operatietijd korter is en de uitkomsten vergelijkbaar zijn met het traditionele strippen. Ondanks dat de cryostripping de conventionele stripping procedure verbeterd, mag niet uit het oog worden verloren dat strippen een voor de patiënt belastende ingreep is met risico's van schade aan het omliggende weefsel en wondcomplicaties.

Nieuwe behandeling van varices: endoveneuze laser behandeling.
Eind jaren negentig zijn nieuwe behandelmethodes ontwikkeld gebaseerd op minimaal invasieve technieken. Hierbij wordt gebruikt gemaakt van katheters, voerdraden en andere instrumenten die via een prik in een bloedvat worden ingebracht om vasculaire afwijkingen te behandelen. Deze technieken zijn minder belastend voor de patiënt, minder beschadigend voor het lichaam en kunnen veelal met plaatselijke verdoving en poliklinisch worden verricht. Tevens brengen deze procedures grote cosmetische voordelen met zich mee omdat er geen sneden gemaakt worden. Endoveneuze laser therapie (EVLA), radiofrequente diathermie (VNUS) en duplex geleide echosclerose (DGES) zijn voorbeelden van deze nieuwe behandelmethodes voor patiënten met varices. Bij de endoveneuze laser behandeling is geen operatiekamer nodig. Ook is regionale of narcose niet nodig, maar kan de behandeling worden uitgevoerd onder tumescent plaatselijke verdoving. Onder duplex geleiding

wordt de VSM aangeprikt, juist onder de knie en een voerdraad wordt opgeschoven tot aan de lies. Over de voerdraad wordt een manteldraad geschoven en de voerdraad wordt uitgenomen. Door de manteldraad wordt vervolgens een glasvezeldraad ingebracht. De tip van de glasvezeldraad steekt daarbij 2 cm uit de manteldraad en wordt onder duplex geleiding geplaatst op een centimeter voor de overgang van de VSM in de vena femoralis. Dan wordt een tumescent verdovingsvloeistof, wederom onder duplex geleiding, rondom de VSM aangebracht. Het doel van deze vloeistofmantel is driedelig: het bewerkstelligen van lokale verdoving, het verminderen van de diameter van de VSM en het beschermen van het omliggende weefsel. Tenslotte wordt de VSM van de lies tot voorbij de knie met de laser ingebrand. Dit proefschrift beschrijft het werkingsmechanisme van de endoveneuze laser behandeling onderzocht in de afdeling Klinische Fysica van het Universitair Medisch Centrum Utrecht en vergelijkt de resultaten van deze techniek met de cryostripping procedure. Dit onderzoek werd uitgevoerd bij patiënten met varices van de saphena magna in de periode 2003-2005 in het Mesos Medisch Centrum te Utrecht.

In **Hoofdstuk 2** beschrijven we de het werkingsmechanisme van de laser in een proefopstelling. Het laserlicht wordt geabsorbeerd door bloed wat resulteert in de vorming van een coagulum rond de tip van de laserdraad. Bij voortdurende laser blootstelling vaporiseert het bloed. De stoombellen worden geïncorporeerd in het coagulum wat resulteert in een isolerende laag rond de tip van de laserdraad. Het laserlicht wordt nu geabsorbeerd in het met stoombellen geïncorporeerde coagulum. Het bloed dissocieert en er ontstaan zwarte flarden in het coagulum en op de tip van de laserdraad kenmerkend voor carbonisatie. Efficiënt worden stoombellen gegenereerd die zich verspreiden door het bloedvat en de binnenkant van de ader tot 100^{0}C voor enkele seconden verhitten. Het volume van de stoombellen is rechtevenredig met de hoeveelheid afgegeven laserenergie. De intraluminale thermokoppels registreren een aanzienlijke temperatuur gradiënt van binnen naar buiten het vat. Zeer locale hoge temperaturen(> 1200 ^{0}C) aan de tip van de laserdraad, temperaturen rond 80 ^{0}C in het lumen van het vat, en vrijwel normale lichaamstemperaturen op 5 mm buiten het vat. De temperatuursverhoging blijft gedurende enkele seconden aanwezig alvorens geleidelijk te dalen tot de uitgangswaarde van de thermokoppels. Deze uitkomsten zijn bevestigd in het weefselmodel met gebruikmaking van thermische beeldvorming gebaseerd op de Schlieren technieken. Dus, de toepassing van endovenous laser veroorzaakt een heterogene verhitting van de vaatwand door intraluminale verspreiding van stoombellen die ontstaan zijn door een isolerend coagulum gevormd rond het uiteinde van de laserdraad. Gebaseerd op deze bevingen postuleren we een 4 fasen model voor het mechanisme van EVLA : coagulatie, vaporisatie, carbonisatie en verhitting van de vaatwand gekenmerkt door een temperatuur gradiënt van binnen naar buiten.

Hoofdstuk 3 beschrijft de techniek van de laserbehandeling en de resultaten van de eerste groep patiënten 2 jaar na EVLA van de vena saphena magna. De studiegroep (85 patiënten, 100 benen) bestaat uit patiënten met ongecompliceerde varices, recidief varices en een enkele patiënt heeft zelfs een open beenwond. De VSM wordt juist onder de knie aangeprikt waarna de laserdraad wordt opgevoerd tot 1 cm voor de overgang van de VSM in het diepe systeem. Hierna wordt de VSM, vanaf de lies tot even onder de knie, omgeven met 250 ml (verdoving)vloeistof. Vervolgens wordt met een 810 nm diode laser (12 watt) een intermitterende laserlicht (1 seconde aan, 1 seconde uit) afgegeven aan de tip van de laserdraad. De laserdraad wordt teruggetrokken met een snelheid van 3-5 pulsen per cm zodat in totaal 36-60 Joules per cm VSM wordt afgegeven. Nadat de laserdraad en de katheter zijn verwijderd wordt een lange elastische kous met een druk van 20-30 mm HG om het been aangebracht en kunnen de dagelijkse activiteiten worden hervat. In 78 (91.8 per cent) patiënten is de procedure succesvol verlopen. In 7 patiënten was het niet mogelijk een laserbehandeling uit te voeren: onduidelijke afbeelding van de laserdraad in de lies (n=3), onmogelijkheid om laserdraad op te voeren naar de lies wegens een vernauwde (n=1) of een erg kronkelend verlopend VSM (n=2), en in twee gevallen ligt de voerdraad na perforatie van de VSM buiten het vat. Ernstige complicaties zijn niet waargenomen. Minder ernstige en tijdelijke complicaties zijn: bloeduitstorting (31%), trekkend gevoel aan de binnenkant van het been (17%), pijn (14%), verharding (2%), en aderontsteking (2%). Het percentage volledige afgesloten VSM's bij Duplex onderzoek 3 maanden na EVLA is 84% en het percentage VSM's zonder terugstroom is 89%. Recanalisatie werd niet waargenomen in 61 VSM's beschikbaar voor controle twee jaar EVLA na behandeling. Het percentage tevreden patiënten na 1 en 2 jaar EVLA is 98% en 92%. Uit de resultaten blijkt, dat EVLA technisch goed en veilig kan worden uitgevoerd, maar dat de toedieningsvorm van laserlicht niet optimaal is. We besluiten dan ook tot een aanpassing in de techniek. De intermitterende afgifte van laserenergie wordt vervangen een continue, waardoor de kans op perforaties van de venenwand is afgenomen en het laserlicht meer uniform wordt afgegeven. Tevens wordt een constante terugtreksnelheid toegepast wat resulteert in het volgende toedieningprotocol: 14 W laservermogen, continue laser toediening en een terugtreksnelheid van de laserdraad van 0.2 cm/s zodat er 70 joules per cm VSM wordt afgegeven. Tevens dient opgemerkt te worden, dat ervaring en kunde in het uitvoeren van de EVLA een belangrijke rol spelen bij het voorkomen van technische en medische problemen.

In **Hoofdstuk 4** worden de resultaten gepresenteerd van een prospectieve gerandomiseerde studie na twee jaar EVLA van de VSM met en zonder crossectomie. Het verrichten van een crossectomie wordt beschouwd als absolute "must" in de chirurgische behandeling van varices. In totaal worden 43 patiënten met ongecompliceerde dubbelzijdige varices geopereerd, waarbij in één zitting beide benen zijn behandeld met EVLA. In één van beide benen is, na randomisatie, aanvullend een crossectomie verricht. In de EVLA groep zonder crossectomie zijn 38 (84%) van de

behandelde VSM's volledig afgesloten en in de EVLA met crossectomie 42 (97.7%). De verschillen tussen beide methodes zijn niet significant. Bij duplex onderzoek, is het percentage recidief varices vanuit de lies na twee jaar 9,3 % in de EVLA groep zonder crossectomie en in de EVLA groep met crossectomie 11.6 %. Een belangrijk verschil is dat de recidieven in de EVLA groep zonder crossectomie het gevolg zijn van hernieuwde terugstroom in de niet afgebonden zijtakken in de lies en dat de recidieven in de EVLA met crossectomie groep het gevolg zijn van neovascularisatie ontstaan in de lies. Het cumulatieve percentage patiënten zonder recidief varices 2 jaar na behandeling is 83.3% in de EVLA groep zonder crossectomie en 87.4% in de EVLA groep met crossectomie. Significante verbetering van klachten en symptomen, gemeten met de venous clinical severity score (VCSS) is in beide behandelingen bereikt, maar er is geen significant verschil tussen beide groepen. Het percentage complicaties is klein en vergelijkbaar; 4 patiënten hebben een wondinfectie na crossectomie. Het achterwege laten van een crossectomie tijdens EVLA lijkt de effectiviteit op de korte termijn niet nadelig te beïnvloeden. Of crossectomie resulteert in een slechtere lange termijn uitkomst wegens neovascularisatie moet worden onderzocht in studies met meer patiënten en langere follow-up.

In **Hoofdstuk 5** worden de resultaten gepresenteerd van een prospectieve gerandomiseerde studie na twee jaar EVLA versus cryostripping. 120 patiënten met ongecompliceerde spataderen zijn na randomisatie verdeeld in twee gelijke groepen: 60 EVLA procedures en 60 cryostripping procedures. In deze periode zijn alle patiënten regelmatig vervolgd met klinisch en duplex onderzoek en een standaard vragenlijst. In the EVLA groep, is de VSM met duplex onderzoek volledig afgesloten in 57 (95%) patiënten en in de cryostripping groep is de introductie van de probe en extractie van de VSM in 100% volledig. EVLA is significant gunstiger dan cryostripping met betrekking tot operatietijd (17 versus 24 min), postoperatieve pijn, niet alleen in aantal (pijnvrije patiënten: 45 versus 15 patiënten) maar ook in maat (VAS score: 2.9 versus 4.4), beperking in dagelijkse activiteit (patiënten met 100% activiteit score: 75 versus 45) en patiënt tevredenheid (zeer tevreden zijn (+3): 64.3% versus 32.7%). EVLA is ook beter, maar niet significant beter, met betrekking tot het voorkomen van complicaties en recidieven (recidiefvrij 77.4 % versus 66.0 %). De recidieven in de EVLA groep zijn het gevolg zijn van hernieuwde terugstroom in de niet afgebonden zijtakken in de lies (n=6) en de recidieven in de cryostripping groep zijn het gevolg van neovascularisatie ontstaan in de lies (n=11). De scores voor VCSS en de Aberdeen Varicose Vein Severity Score, een maat voor kwaliteit van leven, zijn in beide groepen na de behandeling significant verbeterd in vergelijking met voor de behandeling, maar de verschillen tussen beide groepen zijn niet significant. Uit de resultaten van deze studie blijkt dat beide behandelmethoden even effectief zijn, maar EVLA levert beduidend betere resultaten met betrekking tot cosmetiek, postoperatief welbevinden, beperking in dagelijks activiteit, patiënt tevredenheid en minder recidiefkans tot 2 jaar.

In **Hoofdstuk 6** presenteren we de resultaten van een prospectieve gerandomiseerde vergelijking van kosten en kosteneffectiviteit van cryostripping versus EVLA 2 jaar na behandeling. De kosten van dagbehandeling zijn hoger door hogere kosten van de operatiekamer en kosten van ziekenhuisverblijf. Echter, de kosten voor aanschaf van apparatuur voor EVLA zijn hoger dan voor cryostripping wegens de aanschaf van een laser apparaat en een Duplex apparaat terwijl voor cryostripping alleen een cryoapparaat nodig is. De kosten van de EVLA kit zijn significant hoger dan de kosten van het gebruik van de cryoprobes. Patiënten in de cryostripping groep hervatten hun werkzaamheden na gemiddeld 2.2 (0-14) dagen en patiënten in de EVLA groep na 1.3 (range 0-6) dagen. De kosten wegens productiviteitsverlies zijn € 17812 in de cryostripping groep and € 10262 in the EVLA groep. Er is geen verschil in effect gevonden tussen beide groepen gemeten met de SF-6D (een kwaliteit van leven vragenlijst ingevuld 6, 12 en 24 maanden na behandeling. EVLA is geassocieerd met € 132 extra kosten per patiënt (€2783 versus € 2651) en 1.60 Quality Adjusted Life Year's (QALY's) in vergelijking tot 1.59 na cryostripping. Specifieke bootstrap analyse gericht op de (on)zekerheid van onze resultaten toont dat wij met 53% zekerheid kunnen stellen dat EVLA resulteert in een beter uitkomst in termen van kwaliteit van leven maar tegen hogere kosten. Wanneer we een poliklinische cryostripping vergelijken met een poliklinische EVLA procedure en een 50% verlaging in de kostprijs van de laserkit, dan resteert er nog maar een minimaal verschil in de kosteneffectiviteitratio van 46 €/QALY (1681€/QALY versus 1623 €/QALY).

In **Hoofdstuk 7** worden de risico's van lymfatische schade vergeleken van 17 endoveneuze laser behandelingen en 16 cryostripping behandelingen. Beide procedures hebben geen complicaties en geen van de patiënten heeft klachten. Voor de behandeling en 6 maanden na de behandeling werd een lymfklierscintigrafie verricht en beoordeeld door een onafhankelijke onderzoeker die niet geïnformeerd is over de aard van de ingreep. In geen van de 17 EVLA patiënten en in één (6.3%) van de 16 cryostripping patiënten is een onderbreking van de lymfbaan rond de knie en een abnormaal uptake na 120 minuten van het radiopharmacon in de lies waargenomen. Hoewel de aantallen in deze studie te klein zijn om een conclusie te trekken, lijkt bij EVLA de kans op lymfschade kleiner te zijn dan bij cryostripping.

In **Hoofdstuk 8** worden de resultaten gepresenteerd van een histologisch onderzoek na endoveneuze laser behandeling van de vena saphena magna in het onderbeen van 6 patiënten zonder varices voorafgaand aan een amputatie van het onderbeen wegens irreversibel weefselverlies ten gevolge van chronisch obstructief perifeer vaatlijden. Er is gelaserd met verschillende laser powers (14 Watt en 10 Watt) en twee laser toedieningsvormen (continue en intermitterend). In totaal zijn 216 coupes van behandelde aders vergeleken met 6 coupes van niet behandelde aders. In alle coupes is de binnenste laag van de vaatwand, de intima, beschadigd en is het endotheel ernstig gekwetst of compleet afwezig. Carbonisatie en necrose van de media is zichtbaar als gevolg van direct contact van de tip van de laser met de vaat-

wand. Gehomogeniseerde basofiele verkleuring, coagulatie necrose en verlies van de onderlinge samenhang tussen collageen en spierweefsel is aanwezig in de directe omgeving hiervan. Klontering en condensatie van nucleair materiaal is zichtbaar en is kenmerkend voor verdergaande weefselschade. De buitenste laag van de vatwand toont weinig tot geen schade. Perforaties en perivasculaire bloedingen is slechts in enkele gevallen waargenomen bij VSM's behandeld met 40-80 J/cm en in alle gevallen bij VSM's behandeld met 110-200 J/cm. Er is geen schade van de nervus saphenous waargenomen. Concluderend is er een heel scala aan vaatwandschade aanwezig variërend van oppervlakkige endotheel beschadigingen tot volledige destructie van de vaat wand maar er is geen ernstige schade buiten het vat aantoonbaar.

Conclusies

Deze studie heeft duidelijk aangetoond dat endoveneuze laserbehandeling en cryostripping even effectief is in de behandeling van patiënten met varices van de VSM. Vanuit het perspectief van de patiënt heeft EVLA de voorkeur wegens betere cosmetische resultaten, een beter postoperatief welbevinden, en een mindere beperking in de dagelijkse activiteiten na behandeling. Vanuit het perspectief van de dokter heeft EVLA de voorkeur wegens een kortere operatietijd, minder postoperatieve complicaties en minder recidieven tot 2 jaar na behandeling. Vanuit het perspectief van het CVZ dient EVLA de voorkeur te hebben, omdat de procedure poliklinisch en met plaatselijke verdoving kan worden verricht, is geassocieerd met een grotere patiënttevredenheid en met lagere kosten van verloren productiviteit door een sneller herstel na de ingreep in vergelijking met cryostripping.

Geconcludeerd kan worden dat:

1. De toepassing van endoveneuze laser veroorzaakt een heterogene verhitting van de vaat wand door intraluminale verspreiding van stoombellen die ontstaan zijn door een coagulum gevormd rond het uiteinde van de laserdraad.
2. De endoveneuze laser behandeling is veilig en effectief in de behandeling van varices ten gevolge van reflux in de vena saphena magna.
3. Het achterwege laten van een crossectomie beïnvloedt de korte termijn resultaten van EVLA niet significant. Er is een tendens dat het verrichten van een crossectomie resulteert in een slechtere lange termijn uitkomst ten gevolge van neovascularisatie.
4. EVLA en cryostripping zijn even effectief in de behandeling van varices ten gevolge van reflux in de vena saphena magna. EVLA levert beduidend betere resultaten met betrekking tot operatietijd, cosmetiek, postoperatieve morbiditeit, beperking in de dagelijkse activiteiten en recidiefkansen tot 2 jaar.
5. In termen van kosten per gewonnen QALY (SF-6D) is poliklinische cryostripping de dominante strategie, maar EVLA is geassocieerd met vergelijkbare uitkomsten voor relatief geringe extra kosten.
6. De vraag of EVLA de kans op lymfatische schade kan verbeteren, kan op grond van onze kleine getallen niet worden beantwoord. Op basis van onze eerste

ervaring lijkt deze methode een vermindering van de kans van lymfatische schades te kunnen geven.

7. De vraag of EVLA van de vena saphena magna in het onderbeen veilig en effectief kan worden verricht, kan op grond van onze kleine getallen niet worden beantwoord. Op basis van onze ervaringen lijkt deze methode inderdaad veilig te kunnen worden verricht, maar nader onderzoek is noodzakelijk.

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Curriculum vitae

Ben Disselhoff werd 25 oktober 1951 geboren in Amsterdam. Na het behalen van het HBS-B diploma aan het Alberdinck Thijm College Hilversum studeerde hij geneeskunde aan de Erasmus Universiteit Rotterdam. In 1979 werd het artsexamen behaald en aansluitend startte hij met de opleiding chirurgie in het Zuiderziekenhuis Rotterdam (opleider Dr. G. Olthuis). Van 1986 tot 1990 heeft hij zich verder bekwaamd in de vaatchirurgie in het Catharina Ziekenhuis Eindhoven (opleider Dr. J. Buth) en in het Academisch Ziekenhuis Leiden, nu het Leids Universitair Medisch Centrum (opleider Prof. Dr. J.T. Terpstra en Prof. Dr. H.J. van Bockel). Hij is gecertificeerd door de Nederlandse Vereniging voor Vaatchirurgie. Vanaf 1990 tot 2008 was hij werkzaam als algemeen chirurg met speciale aandacht voor de vaatchirurgie in het Overvecht Ziekenhuis Utrecht, nu het Mesos Medisch Centrum. Vanaf 2007 is hij werkzaam in de Bergman Kliniek Bilthoven en in de Jan van Goyen kliniek Amsterdam.

Deze studie heeft duidelijk aangetoond dat endoveneuze laserbehandeling (EVLA) en cryostripping even effectief is in de behandeling van patiënten met varices van de VSM.

- vanuit het perspectief van de patiënt heeft EVLA de voorkeur wegens betere cosmetische resultaten, een beter postoperatief welbevinden, en een mindere beperking in de dagelijkse activiteiten na behandeling.
- vanuit het perspectief van de dokter heef EVLA de voorkeur wegens een kortere operatietijd, minder postoperatieve complicaties en minder recidieven tot 2 jaar na behandeling.
- vanuit het perspectief van het CVZ dient EVLA de voorkeur te hebben omdat de procedure poliklinische en met plaatselijke verdoving kan worden verricht, is geassocieerd met een grotere patiënttevredenheid en met lagere kosten van verloren productiviteit door een sneller herstel na behandeling.

B.C.V.M. Disselhoff
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