

**Superficial venous reflux:
Assessment and treatment by
endovenous laser ablation (EVLA)**

**Superficial venous reflux: Assessment and treatment
by endovenous laser ablation (EVLA)**

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Doctor of Medicine

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The candidate confirms that the work submitted is his own and that
appropriate credit has been given where reference has been made to the
work of others

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This Thesis is dedicated to my parents Mr & Mrs N. Selvalingam

I. Acknowledgements:

My contribution to this thesis has been:

- I was the principle investigator of all the studies presented in this thesis.
- Gaining ethical and trust managerial approval for the studies
- Creating a comprehensive database to combine my data with that collected by previous/ parallel investigators. Due acknowledgement will be given where their data is included.
This data base was used in the studies given in chapters 3, 4, 6 and 7.
- Treating a significant proportion of patients, collecting data from most patients and analysing data relevant to the studies presented in the chapters 3, 4, 6 and 7.
- I treated all patients, collected data and analysed the data of the RCT presented in Chapter 5
- Performing the basic statistical analysis.
- I created, typed and printed all the chapters of this thesis.

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II. Abstract:

More than 40,000 patients undergo treatment for superficial venous incompetence (varicose veins) in the UK each year. Previously the majority underwent conventional surgery with its associated inconvenience and morbidity. Endovenous laser ablation (EVLA) is a relatively new minimally invasive technique that abolishes superficial venous reflux and is an alternative treatment for some patients. Although early studies have shown it to be safe and effective for great saphenous vein (GSV) reflux there remain many questions relating to optimizing the technique and the range of patients for whom it is suitable.

This thesis evaluates factors that may influence EVLA efficacy for GSV reflux and other sites of deep to superficial venous incompetence (small saphenous, anterior accessory GSV, paradoxical reflux). It also assesses changes in venous haemodynamics after EVLA which has led to recommendations on improving treatment outcomes. Further, a prospective database of patients undergoing EVLA and conventional surgery has been maintained (clinical and duplex ultrasound follow-up at 6, 12 & 52 weeks, quality of life data) which has provided additional evidence on the management of patients with varicose veins.

Briefly, these studies have confirmed that laser energy density (J/cm) is the crucial factor determining successful truncal vein ablation following EVLA and that appropriate patients can continue warfarin therapy without compromising the safety or efficacy of treatment.

Other studies demonstrate the transition of ablated truncal veins from a non-compressible “thrombosed” vein to becoming non-visible 1 year after EVLA. Further, sapheno-femoral junction (SFJ) tributaries remain patent and competent with no adverse impact on clinical outcome whilst SFJ neo-vascularisation occurs much less often after EVLA than surgery.

In patients with persistent below-knee GSV incompetence after EVLA residual symptoms are more likely and there is a greater need for sclerotherapy for residual varicosities. A RCT subsequently confirmed that extended ablation of the below-knee GSV achieved superior outcomes.

III. Published articles from this thesis:

Chapter 3:

- **Theivacumar NS**, Dellagrammaticas D, Darwood RJ, Gough MJ. Factors influencing the effectiveness of endovenous laser ablation (EVLA) in the treatment of great saphenous vein reflux. *Eur J Vasc Endovasc Surg.* 2008;35(1):119-23
- **Theivacumar NS**, Gough MJ. Influence of Warfarin on the Success of Endovenous Laser Ablation (EVLA) of the Great Saphenous Vein (GSV). *Eur J Vasc Endovasc Surg.* 2009; 38: 506-510.

Chapter 4

- **Theivacumar NS**, Dellagrammaticas D, Darwood RJ, Mavor AI, Gough MJ. Fate of the Great Saphenous Vein Following Endovenous Laser Ablation: Does Re-canalisation Mean Recurrence? *Eur J Vasc Endovasc Surg* 2008; 36, 211-215.
- **Theivacumar NS**, Dellagrammaticas D, Beale R, Mavor AIM, Gough MJ. The fate and clinical significance of sapheno-femoral junction tributaries following endovenous laser ablation of great saphenous vein. *Br J Surg* 2007; 94:722-725.
- **Theivacumar NS**, Darwood RJ, Dellegrammaticas D, Mavor AI, Gough MJ. The clinical significance of below-knee great saphenous vein reflux following endovenous laser ablation of above-knee great saphenous vein. *Phlebology.* 2009;24(1):17-20.

Chapter 5

- **Theivacumar NS**, Dellagrammaticas D, Mavor AI, Gough MJ. Endovenous laser ablation (EVLA): Does standard above-knee great saphenous vein ablation provide optimum results in patients with both above and below knee reflux? A randomized controlled trial. *J Vasc Surg* 2008; 48: 173-8.

Chapter 6

- **Theivacumar NS**, Beale R, Mavor AIM, Gough MJ, Initial experience in endovenous laser ablation (EVLA) of varicose veins due to small saphenous vein reflux; *Eur J Vasc Endovasc Surg*; 2007;33:614-84
- **Theivacumar NS**, Darwood RJ, Gough MJ. Endovenous laser ablation (EVLA) of the anterior accessory great saphenous vein (AAGSV): abolition of sapheno-femoral reflux with preservation of the great saphenous vein. *Eur J Vasc Endovasc Surg*. 2009;37(4):477-81.
- **Theivacumar NS**, Dellagrammaticas D, Mavor AIM, Gough MJ. Endovenous Laser Ablation (EVLA) of Great Saphenous Vein to Abolish “Paradoxical Reflux” in the Giacomini Vein: A short Report. *Eur J Vasc Endovasc Surg* 2007; 33:614-618.
- **Theivacumar N S**, Gough MJ. Endovenous laser ablation (EVLA) to treat recurrent varicose veins. *Eur J Vasc Endovasc Surg* 2011; 41:691-696.

Chapter 7

- **Theivacumar NS**, Darwood R, Gough MJ. Neovascularisation and recurrence 2 years after varicose vein treatment for sapheno-femoral and great saphenous vein reflux: a comparison of surgery and endovenous laser ablation. *Eur J Vasc Endovasc Surg*. 2009;38(2):203-7.

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VII. Commonly Used Abbreviations:

AAGSV	Anterior Accessory Great Saphenous Vein
AK-GSV	Above-knee Great Saphenous Vein
AVVQ	Aberdeen Varicose Vein Questionnaire
AVVS	Aberdeen Varicose Vein Severity Score
BMI	Body Mass Index
BK-GSV	Below-Knee Great Saphenous Vein
CEAP	Clinical- Etiology – Anatomy – Pathology
CVI	Chronic Venous Insufficiency
DST	Doppler Spectral Trace
DUS	Duplex Ultrasound Scan
DVT	Deep Vein Thrombosis
EVLA	Endovenous Laser Ablation
EVSA	Endovenous steam ablation
EVL ^T	Endovenous Laser Therapy (trademark)
FV	Femoral vein
GA	General Anaesthetic
GSV	Great Saphenous Vein
H&E	Haematoxylin and Eosin
IQR	Interquartile Range
J	Joules
LA	Local Anaesthetic
MOS	Medical Outcomes Study
MSA	Multiple Stab Avulsions
PE	Pulmonary Embolus
QOL	Quality of Life
RCT	Randomised Controlled Trial

RFA	Radiofrequency Ablation
SF-36	Short Form 36
SFJ	Sapheno-Femoral Junction
SFJL	Sapheno-Femoral Junction Ligation
SMC	Smooth Muscle Cell
SPJ	Sapheno-Popliteal Junction
SR	Sirius Red
SSV	Small Saphenous Vein
STD	Sodium Tetra-Decyl Sulphate
TA	Tumescent Anaesthesia
USS	Ultrasound Scan
VAS	Visual Analogue Score
VCSS	Venous Clinical Severity Score
W	Watts

Chapter 1:

1. Introduction and literature review

Varicose veins (VVs) are unsightly dilated and tortuous superficial veins mainly occurring in the lower limbs and often associated with chronic venous insufficiency (CVI). Although varicose veins are common, affecting 30-40% of the population (Evans et al., 1998), many remain asymptomatic and only a proportion present for treatment. Nonetheless a significant component of health care resource is consumed in performing about 40,000 National Health Service operations in the UK each year at an estimated cost of £20-£25 million (Dept. of Health, 2001).

1.1 Epidemiology

Varicose veins are predominantly a condition encountered in Western societies, and their incidence increases with age (Evans et al. 1994). About 32% of women and 40% of men, in the Edinburgh Vein Study (Evans et al., 1998), had truncal varicosities. However, other studies have found the gender difference reversed with a prevalence of 20-25% in women and 10-15% in men (Callam, 1994). Women tend to be over-represented in clinical studies as they are more likely to present with varicose veins because of cosmetic concerns. They are also more likely to undergo treatment.

1.2 Anatomy

The veins of the lower extremity are conventionally divided into the deep and superficial venous systems. These two venous systems are best thought of as components, along with the calf muscles, of a complex vascular reservoir and pump system.

Superficial venous system of the lower extremity

The superficial venous system is composed of a complex web of subcutaneous collecting veins and the thicker-walled conduits or truncal veins of the saphenous systems. The collecting veins are thin-walled structures that are superficial to the saphenous fascia. They gather the blood from the skin and subcutaneous tissue, act as capacitance reservoirs, and passively drain into perforator or truncal superficial veins, called saphenous veins.

The great saphenous vein (GSV) and its tributaries represent the most important veins of the superficial venous system (Figure 1.1). The GSV begins as the medial continuation of the dorsal venous arch in the foot, travels anterior to the medial malleolus, and ascends the medial aspect of the leg, ultimately draining into the deep system at the sapheno-femoral junction (SFJ), which is normally situated some 4cm infero-lateral to the pubic tubercle. The GSV ascends the leg in the saphenous compartment, which is a subcutaneous space that is superficial to the muscular fascia and deep to the saphenous fascia in the leg and thigh (Wendell-Smith, 1997; Caggiati, 1999; Caggiati et al., 2002). The saphenous fascia is a membranous layer of the subcutaneous tissue that is also known as superficial or Scarpa's fascia. The GSV generally has two major tributaries below and above the knee; it also receives blood from the external pudendal, inferior epigastric, and external circumflex iliac veins just before it drains into the femoral vein. Although, the GSV has been said to be duplicated in as many as 20% of subjects, the incidence of true duplication is much lower (Ricci and Caggiati, 1999). However, large extra-fascial tributary veins, which are termed accessory saphenous veins, can run parallel to the GSV and can functionally act as duplicated veins (Ricci and Caggiati, 1999).

The small saphenous vein (SSV) is the other principle truncal superficial vein (Figure 1.2). It begins on the lateral aspect of the foot, travels posterior to the lateral malleolus, and ascends the midline of the calf superficial to the muscular fascia and deep to the saphenous fascia.

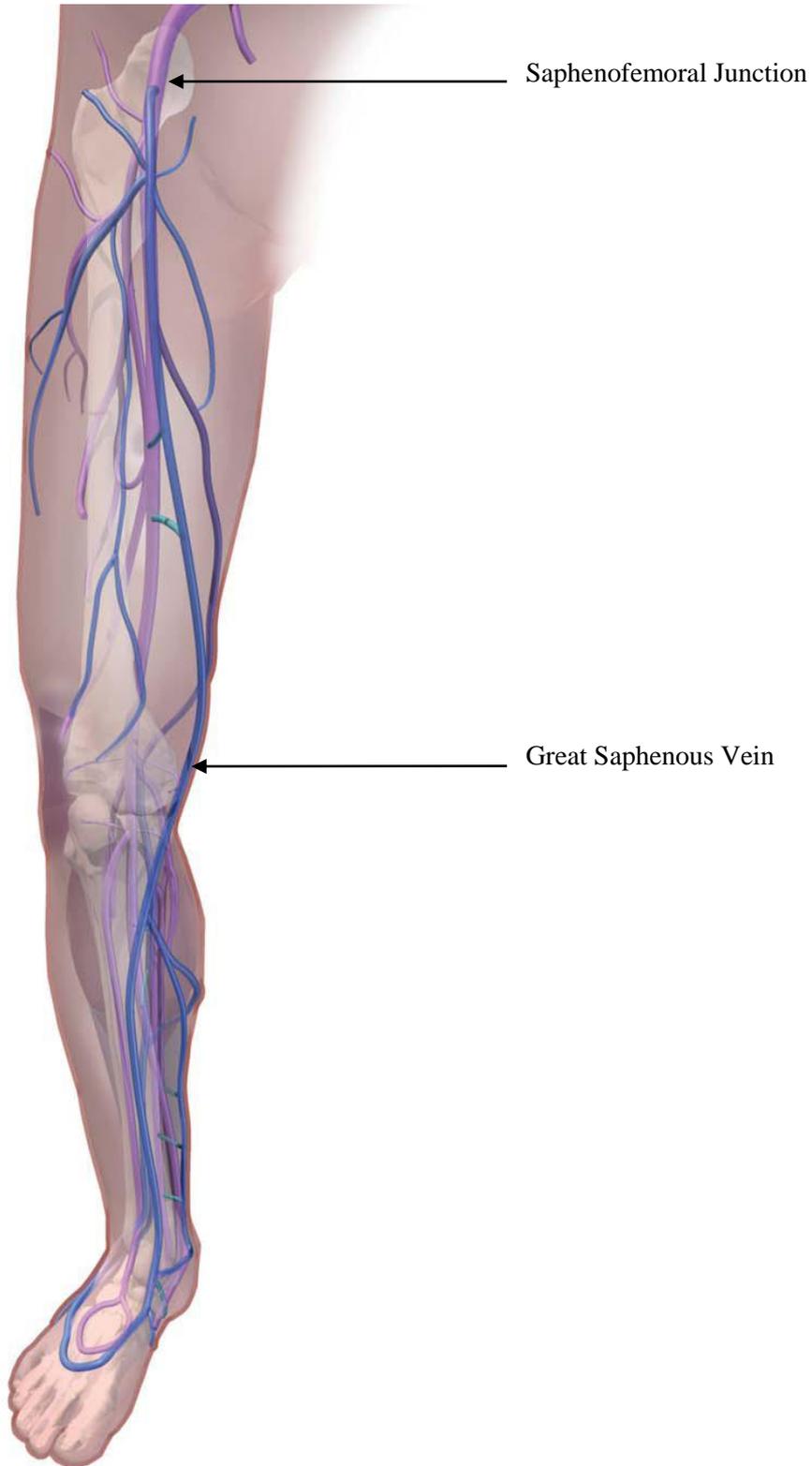


Figure 1.1: Anatomy of the great saphenous vein

(source: American College of Phlebology: http://www.phlebology.org/pdfs/Ch1_pp1-4.pdf)

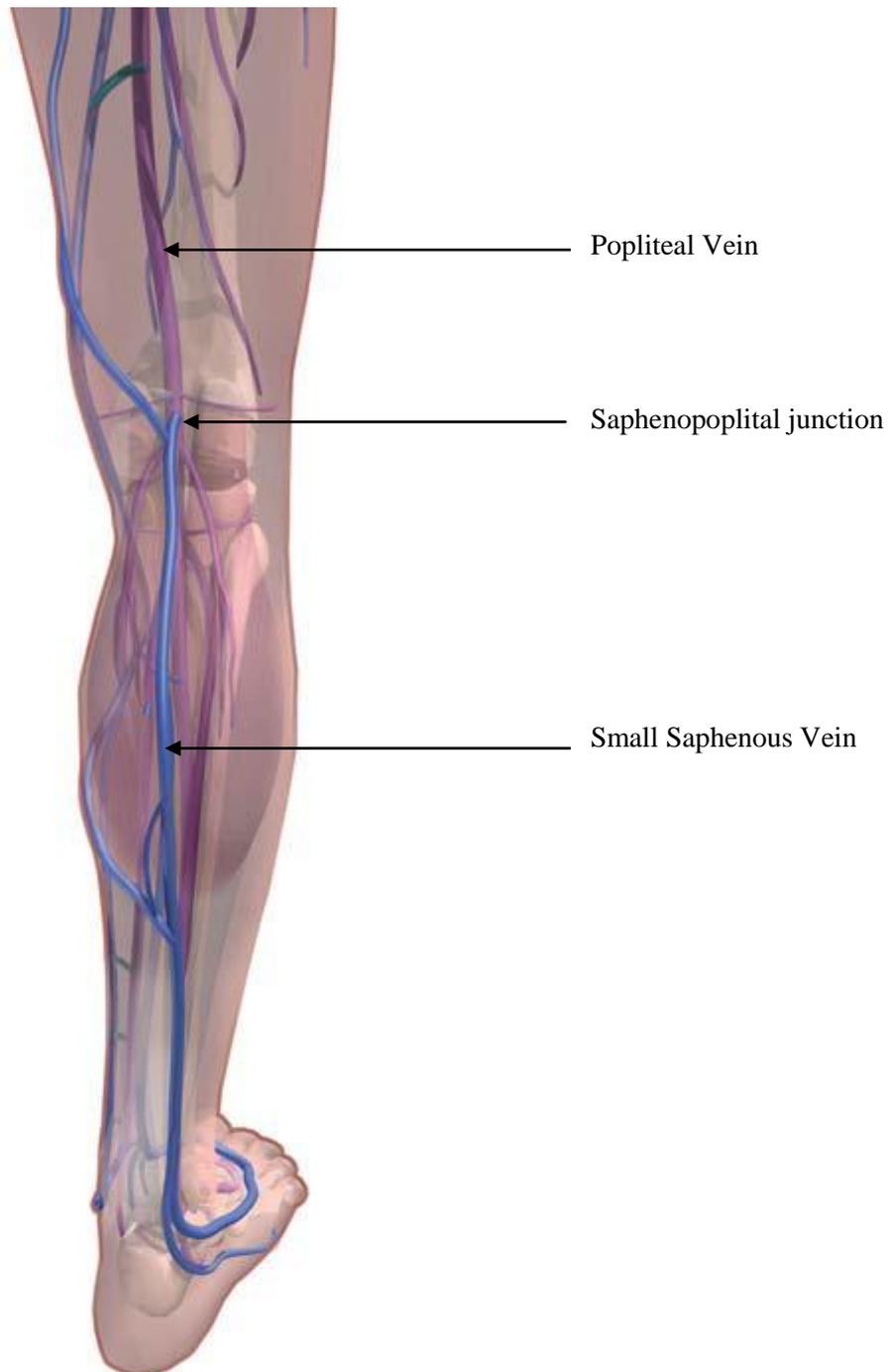


Figure 1.2: Anatomy of the small saphenous vein

(source: American College of Phlebology: http://www.phlebology.org/pdfs/Ch1_pp1-4.pdf)

In the majority ($\approx 2/3$) of subjects, the SSV drains into the popliteal vein just above the knee via the sapheno-popliteal junction (SPJ) (Bergan, 2001). However, the level of the SPJ is much more variable than that of the SFJ and this is an important factor in the failure to perform an adequate ligation of the junction in a proportion of patients undergoing conventional surgery. In as many as one third of the limbs the SSV drains into a posterior medial tributary of the GSV or directly into the GSV (as the vein of Giacomini), or into a deep vein in the thigh via a perforator (Bergan, 2001). In many of these cases of variant drainage, a standard SPJ may also be present. The SSV is truly duplicated in 4% of the limbs; most often this is segmental, primarily involving the mid-portion of the vein (Caggiati, 2001).

Deep venous system of the Lower Extremity

The veins of the deep venous system are deep to the fascial investments of the muscles of the lower limb. They include the planter vein of the foot, three pairs of tibial veins in the calf, and the popliteal and superficial femoral veins behind the knee and in the thigh. In addition, numerous venous sinusoids found within the muscles of the lower limb are important components of this system. Those in the calf are most important and include the soleal and gastrocnemius veins. These sinusoids drain into other deep veins via valved connecting veins. All deep veins are important elements of the pumping system and are responsible for returning blood from muscles, as well as the blood collected from the superficial veins, back to the heart. (Mahadevan, 2008).

Perforating veins

Perforating veins connect elements of the superficial venous system with the deep system. These veins obliquely perforate the deep fascia and connect the collecting and saphenous veins with femoral, popliteal, tibial and sinusoidal veins. The larger perforators contain valves that direct flow from the superficial veins to the deep veins and are often accompanied by a perforating artery. Four groups of clinically important perforating veins have been identified in fairly typical locations and have eponymous names (figure 1.3) (Min et al., 2003).

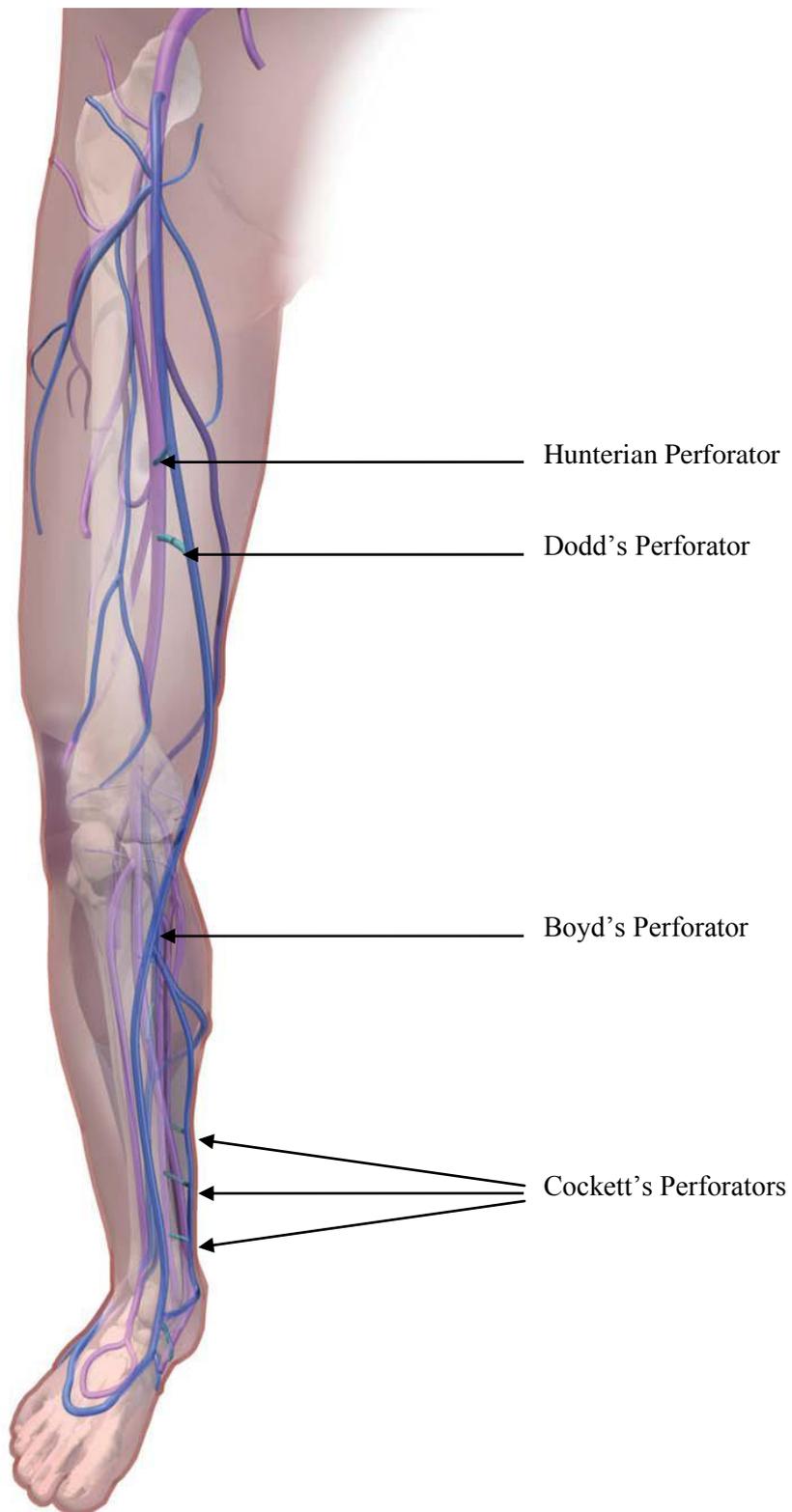


Figure 1.3 Named perforator veins in the lower limb

(source: American College of Phlebology: http://www.phlebology.org/pdfs/Ch1_pp1-4.pdf)

Anterior accessory of great saphenous vein (AAGSV)

A superficial vein accompanying the GSV and situated ventrally to its course on the anterior thigh, but usually not in the saphenous compartment, is called as the AAGSV. To emphasize the difference between the accessory and main GSV, the former is located more superficially, but it can approach the latter in the thigh and enter the saphenous compartment. It most often drains into the GSV within 1 cm of the SFJ (Cavezzi et al., 2005), although different patterns of communication are possible (figure 1.4).

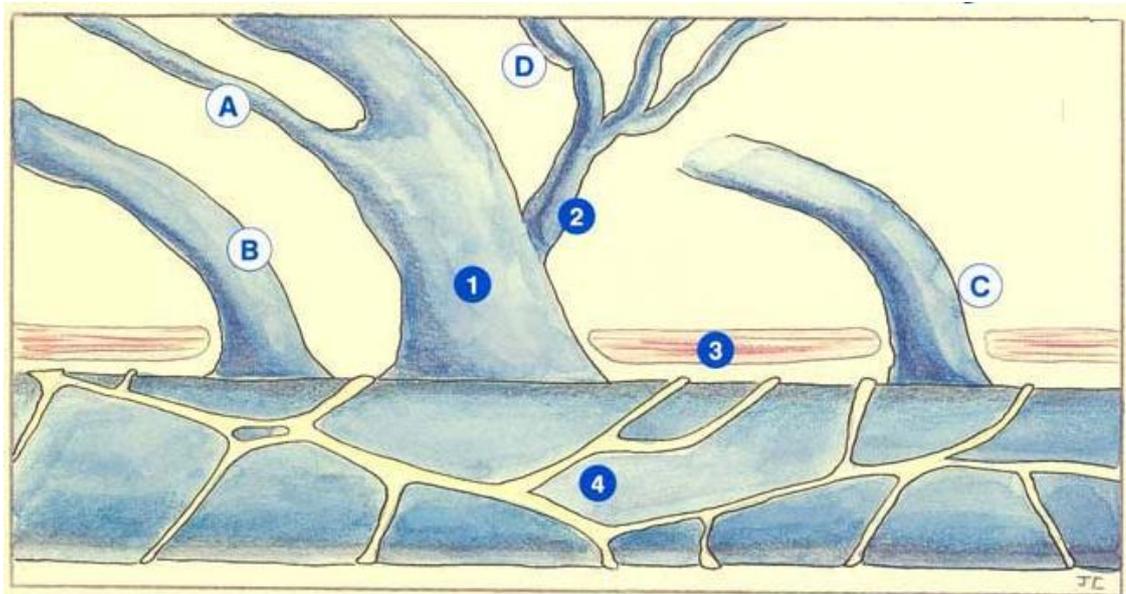


Figure 1.4: Potential communication between the AAGSV and the GSV/deep venous system

(Source: http://www.phlebologia.com/en/saph_access.asp)

AAGSV may drain into the GSV (A), directly into the femoral vein below (B) or above (C) the SFJ, or even into a tributary of the GSV (D).

1: GSV

2: Lateral tributary

3: Cribriform fascia

4: CFV (common Femoral Vein)

New Nomenclature of the superficial veins

In 2001, presidents of the International Union of Phlebology (IUP) and International Federation of Associations of Anatomists (IFAA) nominated an International Interdisciplinary Committee (IIC) to revise the nomenclature of the deep and superficial veins of the lower extremity. IIC issued a document at the pre-congress meeting of the 14th World Congress of IUP, held in Rome (September 2001), with the attendance of members of the Federative International Committee on Anatomical Terminology (FICAT). The document was published as the 'Nomenclature of the veins of the lower limbs: an international interdisciplinary consensus statement' (Caggiati et al., 2002). This was revised in May 2004 at the second meeting in Rome. Figures 1.5 and 1.6 summarise the new nomenclature.

Abbreviations for Figure 1.5 and 1.6:

AAGSV:	Anterior accessory great saphenous vein
AAGSVC:	Anterior accessory great saphenous vein of the calf
ATCV:	Anterior thigh circumflex vein
CESSV:	Cranial extension of small saphenous vein (Gioacomini vein)
DVAF:	Dorsal venous arch of foot
DVNF:	Dorsal venous network of foot
GSV:	Great saphenous vein
ISV:	Intersaphenous vein(s)
MMV:	Medial marginal vein
PAGSV:	Posterior accessory great saphenous vein
PAGSVC:	Posterior accessory great saphenous vein of the calf
PV:	Popliteal vein
PeV:	Perforating veins
PTCV:	Posterior thigh circumflex vein
SCIV:	Superficial circumflex iliac vein
SDMV:	Superficial dorsal metatarsal veins
SDVP:	Superficial dorsal veins of penis ♂
SEPV:	Superficial External pudental vein
SEV:	Superficial epigastric vein

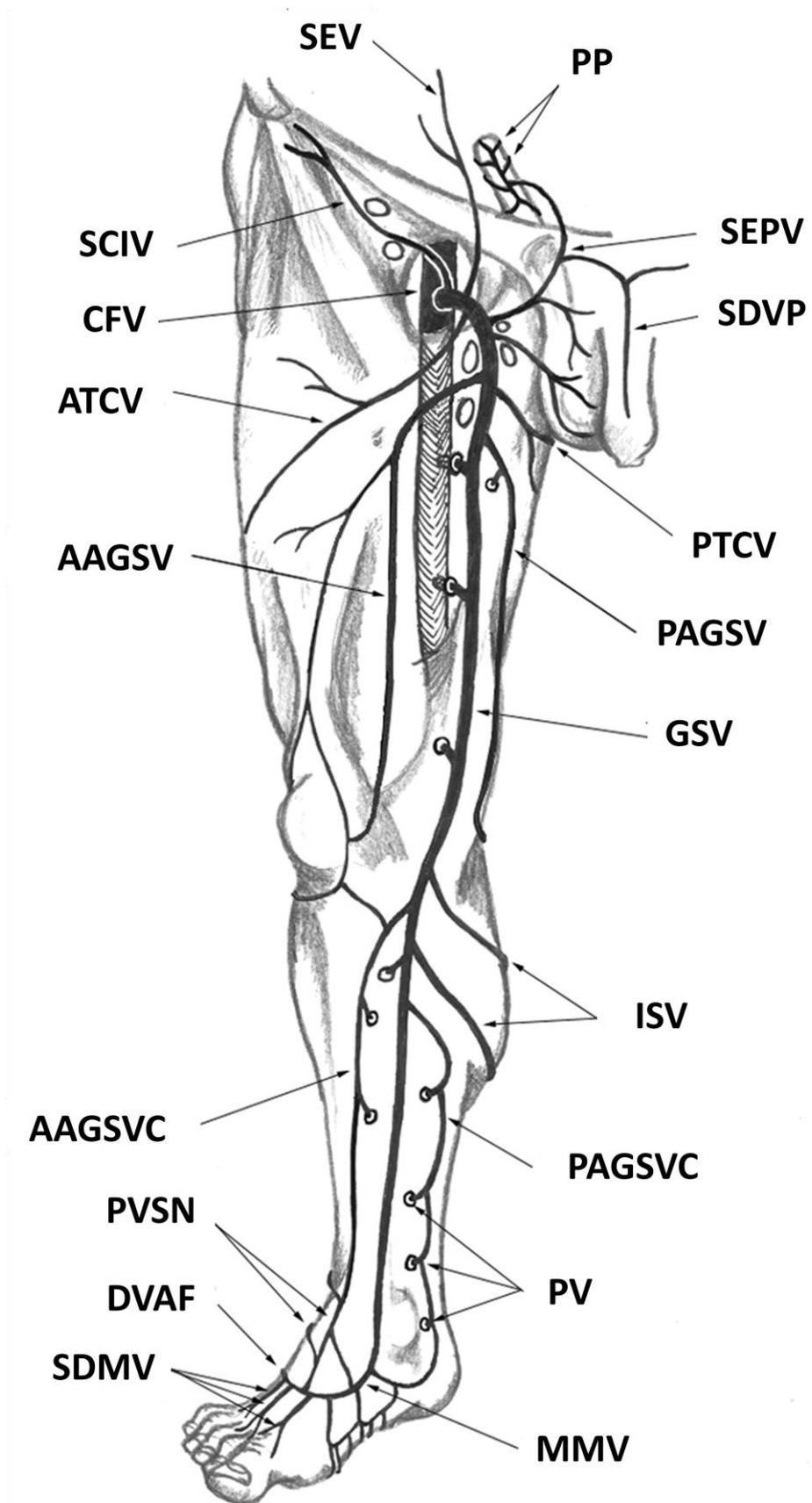


Figure 1.5: New nomenclature for the superficial veins of the lower limb (antero-medial view) (Kachlik et al., 2009)

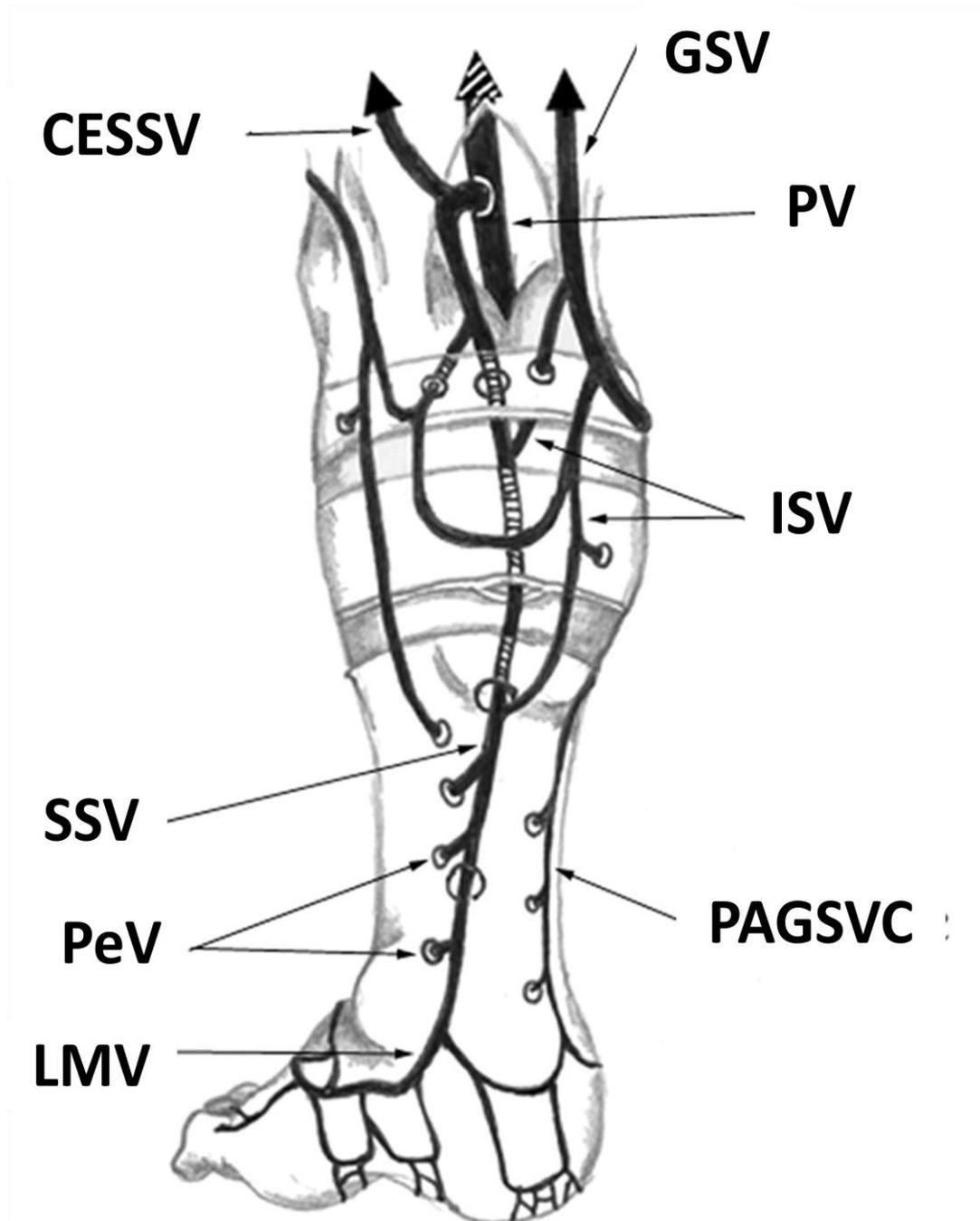


Figure 1.6: New nomenclature for the superficial veins of the lower leg (postero-lateral view) (Kachlik et al., 2009)

1.3 Pathophysiology

The veins in the lower limbs are not passive conduits but rather complex components of a vascular pumping mechanism responsible for actively returning blood to the heart against a substantial gravity gradient. This can be achieved only by in the presence of competent valves, patent venous flow tracts, and a functional venous pump (calf muscles). Incompetent venous valves account for the majority of cases of venous insufficiency. In the erect position, the pressure created by the column of blood increases from the heart down to the ankle. Propagation towards the heart depends on compression of deep veins by calf muscles augmented by functional one-way valves in healthy veins. Thus the calf muscles functions as a “peripheral heart” with the valves in the saphenous veins, perforators and deep veins analogous to the cardiac valves.

Venous insufficiency develops when a component of the venous system fails. With failure, the thin-walled superficial collecting veins are exposed to higher than normal pressures, causing dilatation and elongation, resulting in varicose veins. Valvular dysfunction, particularly in the superficial veins, is the most frequent cause of varicose veins in patients without skin changes or oedema. Venous obstruction and deep venous insufficiency are more frequent in patients with varicosities associated with skin changes and may follow a previous deep vein thrombosis. Dysfunction of calf pump is the least common cause of varicose veins (Labropoulos et al., 1996).

Valvular Insufficiency

The pattern of venous reflux related to incompetent veins depends on which valves fail and through which pathway the leaking blood finds its way to the deep venous system or into the varicosities. Incompetence of the SFJ and GSV is the most common cause of significant varicose veins and is responsible for about 60-70% of cases whilst SPJ and SSV reflux accounts for their development in some 30% of patients (Labropoulos, 1994a). Of the remainder

perforator incompetence is the cause in most instances. These different patterns of reflux may occur on their own, or in combination with each other. A small proportion of varicosities arise because of incompetence of pelvic veins (ovarian vein, tributaries of the internal iliac vein).

Incompetence within the tributaries of the GSV can also lead to varicose veins. These include the anterior accessory great saphenous vein (AAGSV) and posterior-medial tributary reflux, which may or may not be associated with SFJ incompetence.

Venous Obstruction

Deep vein thrombosis, intrinsic venous stenosis (May-Thurner Syndrome) and external compression (pelvic tumour) are the main causes for venous obstruction. When the calf muscle pump functions normally, it generates sufficient pressure to move blood against gravity. However, if the outflow tract is obstructed, pressure elevations can result in dilatation and secondary valvular incompetence. These forces may lead to perforator incompetence and subsequent venous hypertension and secondary superficial venous insufficiency leading to chronic venous insufficiency (CVI). CVI due to venous obstruction will not be considered in this thesis as the treatment strategy is different for these patients.

1.4 Risk factors and aetiology of varicose veins

The pathogenesis of primary varicose veins is almost certainly multi-factorial and it has been suggested that both genetic and acquired factors may underlie their development (Cornu-Thenard et al., 1994; Chiesa et al., 2005). Pregnancy has an association with the development of a variety of venous disorders including spider teleangiectasia and varicose veins (Sadick, 1992) affecting 10-20% of pregnant women (Sumner, 1981). The diameters of both competent and incompetent superficial veins increase during pregnancy and decrease postpartum, gradually returning to their baseline values (Boivin et al., 2000). It has been suggested that hormonal or

other systemic factors may play a role in the development of postpartum varicose veins (Cordts and Gawley, 1996; Mashiah, 1999).

Despite the widely held belief that pregnancy may be an important aetiological factor in the development of superficial venous incompetence there is some evidence that this merely promotes the development of varicosities in patients with pre-existing venous insufficiency (Sparey et al., 1999).

Other evidence has implicated diet as having a role in the development of varicose veins although the available literature does not allow a firm conclusion to be made (Adhikari et al. 2000). Despite these hypotheses a recent demographic study supports a multi-factorial aetiology with characteristics such as sex, advanced age, number of pregnancies, and family history of venous disease all contributing to their development (Chiesa et al., 2005). The relative contribution of each of these risk factors is difficult to ascertain although further demographic evidence from the Framingham study indicate that obesity, high systolic blood pressure, cigarette smoking and low levels of physical activity may also be important (Brand et al., 1988).

1.5 Symptoms & complications

The relationship between varicose veins and symptoms is controversial. Whilst it has been suggested that they might cause aching, heaviness, pruritus, and oedema (Browse, 1999) asymptomatic superficial venous reflux (duplex ultrasound) is present in up to 39% of the population (Labropoulos et al., 1995; Labropoulos et al., 1996). In the Edinburgh Vein Study lower limb symptoms were common irrespective of the presence of varicose veins with 48% of all women complaining of aching legs. Pruritus was positively associated with the severity of varicosities in men and similarly heaviness, aching and itching in women. However the level of agreement between symptoms and truncal vein incompetence was too low to be of clinical

value. Further, the majority of lower limb symptoms seemed to have a non-venous cause (Bradbury et al., 2000).

In another study Labropoulos et al reported that 70% of patients with GSV reflux complained of aching legs and this was more common with full-length GSV incompetence compared to above or below knee reflux alone. Ankle swelling was also more likely with more prolonged (more severe) reflux (Labropoulos et al., 1994a). A minority of patients ($\leq 5\%$) with varicose veins develop complications including thrombophlebitis, varicose eczema, lipodermatosclerosis and ulceration (Tibbs, 1996).

Although it has previously been suggested that an earlier deep venous thrombosis (DVT) was responsible for almost all cases of venous ulceration this view was proposed before ultrasound assessment of the venous system was widely available (Christopoulos, 1989). Subsequently it has become clear that both deep and superficial venous incompetence can result in the skin changes of advanced venous insufficiency either alone or in combination (Labropoulos et al., 1996).

1.6 Disease severity

Based upon their appearance varicose veins are categorized as telangiectasia, venulectasia, reticular veins, and non-saphenous and saphenous varices, depending on their size and location (intradermal or subcutaneous). In this thesis “disease severity” associated with superficial venous incompetence was assessed using the methods described below.

1.6.1 CEAP classification

In 1995 an international committee of the American Venous Forum produced a consensus document for the classification and grading of chronic venous disease, the CEAP classification (Porter and Moneta, 1995) which was formally endorsed by the American Venous Forum, the Joint Council of the Society for Vascular Surgery and the North American-International Society for Cardiovascular Surgery. Thus it is widely used as a clinical method of assessing the severity of venous disease. The basis for this classification is shown in Table 1.1 with limbs classified according to clinical signs (C), cause (E), anatomic distribution (A), and pathophysiology (P). In general, the most discriminatory information about disease severity in an individual patient is derived from the “C” grade (Table 1.2).

	Definition
C	Clinical signs (grade 0-6), supplemented by (s) for symptomatic and (a) for asymptomatic presentation
E	Etiologic Classification (Congenital, Primary, Secondary)
A	Anatomic Distribution (Superficial, Deep, or Perforator, alone or in combination)
P	Pathophysiologic Dysfunction (Reflux or Obstruction, alone or in combination)

**Table 1.1: CEAP classification of chronic lower extremity venous disease
(Porter & Moneta 1995)**

“C” Class	Clinical signs
C ₀	No visible or palpable signs of venous disease
C ₁	Telangiectasia, reticular veins, malleolar flare
C ₂	Varicose veins
C ₃	Oedema without skin changes
C ₄	Skin changes ascribed to venous disease (pigmentation, venous eczema, lipodermatosclerosis)
C ₅	Skin changes (as defined above) in conjunction with healed ulceration
C ₆	Skin changes (as defined above) in conjunction with active ulceration

**Table 1.2: C of CEAP classification of venous disease in the lower limb
(Porter & Moneta 1995)**

1.6.2 VCSS (Venous clinical severity score)

The American Venous Forum Committee on Venous Outcomes Assessment developed a venous severity scoring system (VCSS) based on the most representative elements of the CEAP system (Rutherford et al., 2000). In the VCSS, 9 clinical characteristics of CVI are graded from 0 to 3 using specific criteria to avoid overlap or arbitrary scoring. Finally 0-3 points are added depending upon the use or requirement for active conservative therapy (compression, elevation). This produces a 30-point scale (appendix: B2).

1.6.3 Aberdeen varicose vein severity score (AVVS)

AVVS (Garratt et al., 1993) assesses the impact of the varicose veins on quality of life using a questionnaire comprising 13 validated questions. The assessment includes the extent of the varicosities, symptoms and the impact on quality of life (QOL). A full questionnaire and the methods for calculating the score are included in appendix B3.

1.7 Investigations

The aim of investigations in patients with a clinical diagnosis of varicose veins is to identify the site(s) of venous incompetence responsible for their development.

A number of clinical tests have been described that will give an indication about the principle site of reflux. These have been superseded by more accurate investigations including hand-held Doppler and duplex ultrasound and will not be discussed further.

Hand-held Doppler examination can be easily performed in an out-patient setting and is a useful screening test, particularly for identifying SFJ and GSV reflux where it performs well in comparison to duplex ultrasound (Darke et al., 1997). In contrast it is less reliable for assessing SPJ reflux and may be associated with a significant false positive rate (Kent and Weston, 1998) as a result of detecting reflux in other veins in the popliteal fossa (gastrocnemius veins, popliteal vein, and superficial tributaries of GSV crossing the back of the knee). Further, the location of the SPJ is much more variable than that of the SFJ which confounds the difficulty. Thus duplex ultrasound is the investigation of choice in patients where SPJ/SSV reflux is suspected.

Similarly, hand-held Doppler is unreliable when assessing limbs with recurrent varicose veins for which duplex ultrasound is again required.

For the definitive identification of the source of reflux DUS is the investigation of choice (see below) and is mandatory when assessing patients who have, or are suspected to have had a previous deep vein thrombosis.

Other investigations include ambulatory venous pressure measurements and air-plethysmography. These are essentially research tools used to grade reflux severity and are rarely used clinically. Finally, contrast venography is now obsolete in respect of investigating patients with superficial venous incompetence although it may still be indicated in patients with secondary varicose veins, particularly if an iliac compression syndrome is suspected.

1.7.1 Duplex ultrasound scan (DUS)

DUS of the superficial and deep venous system has emerged as the most accurate and time efficient tool for assessing venous insufficiency. Several studies have demonstrated the effectiveness of DUS in accurately mapping patterns of venous reflux (Welch et al., 1992; Neglen and Raju, 1992; Vlentin et al., 1993; Baker et al., 1993). In addition to demonstrating abnormal venous anatomy/reflux DUS provides reliable and objective follow-up after intervention. Thus it can be used to document complete abolition of reflux in all treated venous segments and to detect and determine the causes of recurrences. Finally DUS is crucial to guiding treatment with the newer minimally invasive techniques.

It should be noted however that colour Doppler imaging during DUS may underestimate the presence of reflux (Araki et al., 1993) and that this is best identified and documented using pulsed-wave Doppler imaging. Although most investigators use the criteria of reverse flow lasting for more than 1.0 second to define significant reflux (Labropoulos et al., 2006), there is no consensus on this. Further, some authors claim that the cut off for duration of reflux should be different for different veins; deep veins in calf: 0.5s, deep veins in thigh: 1s, iliac veins and IVC: 1.5s, perforating veins: 0.35s, superficial vein: 1s. (Sarin et al., 1994; Labropoulos et al.,

2003; Min et al., 200; Neuhardt DL, 2008). In the studies reported in this thesis, reflux >1s in a superficial vein is considered significant. Even though, DUS is widely available and most commonly used to detect venous reflux it does not grade its severity.

Some authors (Kalodiki et al., 1993, Neglen et al., 2004) suggest that a standardised calf compression using a rapid inflation / deflation pneumatic cuff could be used to assess reflux objectively. However, selecting cuff size in relation to different calf size is not practical. An alternative method could be to examine the patient in the 15° reverse Trendelenburg position with the Valsalva manoeuvre to elicit reflux, specifically for the examination of thigh veins (Masuda et al., 1994). The disadvantage is that the test is dependent on a cooperative patient who is able to perform the manoeuvre and the ability to perform the manoeuvre varies among patients.

1.7.2 Objective assessment of reflux severity

There are 3 principle methods that can be used to assess the severity of venous reflux. These are:

- i) measurement of the hydrostatic pressures in a dorsal vein on the foot
- ii) determination of the venous filling index using air-plethysmography
- iii) photoplethysmography

Venous pressure measurements in pedal veins

Although the static venous pressure in the pedal veins is of no use in discriminating venous insufficiency from healthy veins, measurement of ambulatory venous pressure in these veins is a useful tool for objective assessment of the severity of venous insufficiency and varicose veins (Nicolaides and Zukowski, 1986). The ambulatory venous pressure (AVP) is defined as the lowest pressure reached during exercise (ten tip toe movements). Refill time (RT₉₀) is the time

taken to reach the 90% of pre-exercise pedal venous pressure after the exercise (Figure 1.7). These two parameters have been shown to correlate with clinical severity of venous disease and the incidence of related complications (Nicolaidis and Zukowski, 1986).

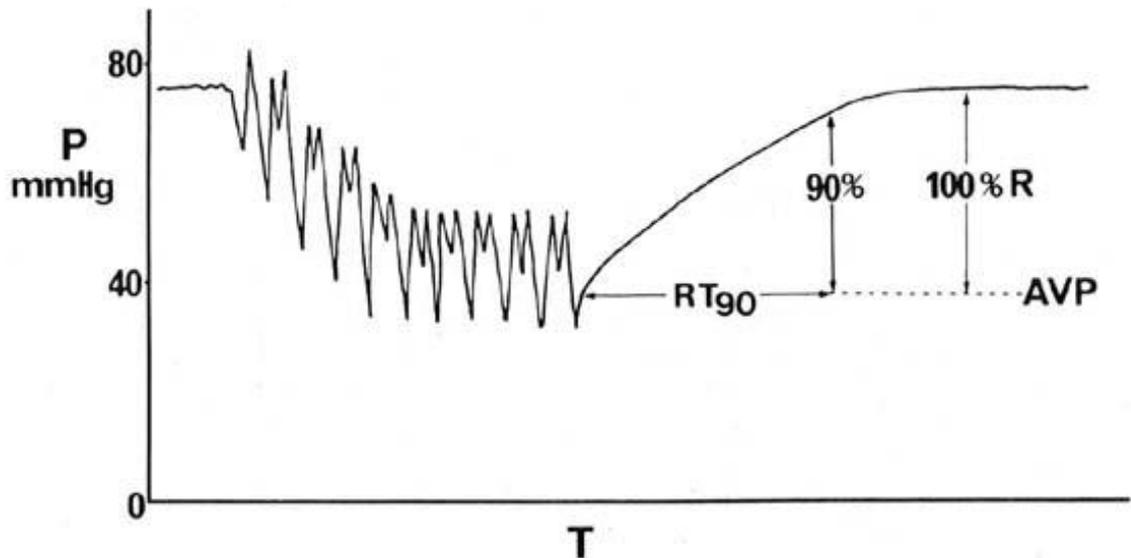


Figure 1.7: Typical venous pressure recording of the effect of 10 tiptoe movements on venous pressure

P = pressure; T = time; R = refilling; RT_{90} = time taken for 90% refilling; AVP = ambulatory venous pressure at the end of exercise

Air-plethysmography (APG)

Air-plethysmography provides quantitative information about various components of the calf muscle pump (Christopoulos et al., 1988 a; Christopoulos et al., 1988 b; Christopoulos et al., 1989). These include the rate of venous filling of the reservoir (venous filling index) as a result of standing; the venous volume, which is the amount of blood in the venous reservoir; the ejected volume, and the ejection fraction as a result of a single tiptoe movement; and the residual volume and residual volume fraction as a result of 10 tiptoe movements. Although, ejection fraction and residual volume fraction were initially considered reproducible, this has been challenged by other authors (Yang et al., 1997; Asbeutah et al, 2005). Venous filling index

(VFI), a measurement of reflux severity has been found to be reproducible and has a good correlation with disease severity (Christopoulos et al., 1988 b).

1.8 Treatment of varicose veins

What is an ideal treatment for varicose veins?

Beale et al described the ideal management for varicose veins as follows (Beale et al., 2005) “The optimum treatment of varicose veins requires accurate identification of the sources of superficial venous reflux. Subsequent treatment, specifically tailored to abolish venous reflux, should relieve any symptoms attributable to superficial venous incompetence, prevent complications, improve cosmesis, be associated with a low morbidity, low recurrence rates, and if possible a short recovery time. The cost-effectiveness of potential therapies should also be considered”.

Treatment options for varicose veins

Treatment options for varicose veins range from non-operative compression hosiery to interventional surgical treatment. Although conventional surgical treatment has long been considered the standard option, the newer minimally invasive techniques are being studied as an alternative to this. The main treatment options are described in table 1.3.

Conservative Treatment	Compression hosiery	Below knee grade II (20-30mmHg) compression stockings
Minimally Invasive (Ablation) techniques	Endovenous laser ablation (EVLA)	<i>Thermal ablation</i> of truncal vein with diode laser (LA), May also require adjuvant phlebectomy or sclerotherapy (local anaesthesia)
	Radiofrequency ablation (VNUS [®]) / Closure Fast [®]	<i>Thermal ablation</i> of truncal vein with radiofrequency (LA), May also require adjuvant phlebectomy or sclerotherapy (local anaesthesia)
	Endovenous steam ablation (EVSA)	<i>Thermal ablation</i> of truncal vein with water steam (LA), May also require adjuvant phlebectomy or sclerotherapy (local anaesthesia)
	Ultrasound guided foam sclerotherapy	<i>Chemical ablation</i> of truncal vein under DUS guidance. May also require adjuvant sclerotherapy for tributary varicosities
Surgery	SFJ ligation + GSV stripping / SPJ ligation ± SSV stripping and phlebectomies / perforator ligation	GA day case or in-patient. Widely available. Variations include length of vein stripped and method of stripping
	Ambulatory conservative haemodynamic management (ACHM or CHIVA)	Identification of sites of deep to superficial reflux and elimination of these sites only (GA)
	Trans-illuminated powered phlebectomy (TIPP, TriVex [®]) as an adjunct to truncal vein ligation /stripping	Alternative treatment to phlebectomies resulting in fewer incisions. SFJ/SPJ ligation still required. (GA)

Table1.3: Treatment modalities for varicose veins

1.8.1 Conservative Treatment / Compression hosiery (CH)

CH exerts pressure over the veins and tissue as defined by the law of Laplace: $P=T/R$; where the pressure (P) exerted by an elastic bandage or stocking is proportionate to its tension (T) and the inverse of the radius (R). Compression pressure is higher on more convex areas (ankle) than in less convex areas (thigh) provided the same tension is maintained. CH is designed to produce the same tension throughout the leg thus providing a pressure gradient from the ankle upwards. Different grades (class 1 to 4) of CH are used for different indications (table 1.4). Contraindications to CH include advanced peripheral arterial disease and septic phlebitis. Although different lengths of CH are available, ankle-knee stockings are more acceptable to many patients (Kiev et al., 1990).

Grades	Indications
Class 1 (18-21 mmHg)	Mild varicose veins (C2) without oedema Early varicose veins in pregnancy
Class 2 (23-32 mmHg)	Commonly used for symptomatic varicose veins and CVI (C3, C4, C5) and after other treatments (EVLA, foam sclerotherapy, surgery)
Class 3 (34-46 mmHg)	Post thrombotic insufficiency, severe CVI (C6) Lymphoedema
Class 4 (>49 mmHg)	Severe lymphoedema Elephantiasis

Table 1.4: Different classes of compression stocking and their main indications (German Standard)

CH aims to reduce or control venous reflux and thus improve symptoms and reduce oedema among patients with varicose veins (Jones et al., 1980; Szendro et al., 1992; Ibegbuna et al., 1997; Zajkowski et al., 2002; Hirai et al., 2002). However as expected, the benefit from CH is restricted to the period during which the stocking is worn (Labropoulos et al 1994b).

A non-blinded randomised controlled trial of compression stockings (grades I and II) in pregnancy showed that the development of GSV reflux and symptoms were less common in the treated group ($p=0.047$) as compared to controls, but that there was no difference in the development of varicose veins (Thaler et al., 2001). The study was not powered to assess differences between grade I and II stockings. Compression therapy may also be facilitated by a variety of proprietary bandages although with the exception of Setopress® (half strength 30mmHg; full strength 40mmHg) the pressure exerted by these is uncertain and difficult to control.

Poor compliance (Kiev et al., 1990), a lack of patient education (Samson and Showalter, 1996) and poor cosmesis are drawbacks to the use of CH. In general, grade II stockings are better tolerated than grade III stockings (Dale and Gibson, 1992) but compliance also varies depending on the manufacturer (Nelson et al., 2003).

1.8.2 Minimally invasive (ablation) techniques

Several minimally invasive techniques are increasingly used to treat varicose veins. All of these avoid traditional surgical incisions, but may require 1-2mm wounds to facilitate cannulation of the target truncal vein. These techniques ablate the target vein in situ rather than removing it (stripping). These methods are summarised in table 1.5.

Thermal ablation	Chemical ablation
Endovenous diathermy	Sclerotherapy (liquid)
Endovenous radiofrequency (VNUS)	Foam sclerotherapy
Endovenous laser ablation (EVLA)	
Endovenous steam ablation (EVSA)	

Table 1.5: Examples of different ablation types

1.8.3 Thermal Ablation Techniques

Endovenous administration of thermal energy is not new. Electrocoagulation was described by O'Reilly in 1977 (O'Reilly, 1977) and endovenous monopolar diathermy was described again in 1994 (Gradman, 1994). Use of endovenous radiofrequency and laser ablation has emerged in the new millennium and these techniques are being refined. Recently Milleret et al (Milleret, 2006) have also described the endovenous steam ablation (EVSA) as an alternative method of delivering thermal energy. However, laser and radiofrequency ablation techniques are currently the most widely used thermal ablation techniques.

1.8.4 Endovenous Laser Ablation (EVLA)

Endovenous laser ablation is a minimally invasive technique and this was initially described by Navarro and Min in 2001 (Navarro et al., 2001). An important potential advantage of EVLA is that it is performed as an outpatient procedure under local anaesthesia. Different types of diode laser (810 - 1470nm wavelength) and a 1064nm Nd:YAG laser have been studied (Navarro et al., 2001; Proebstle et al., 2002; Oh et al., 2003; Goldman et al., 2004). To date 810-940nm diode lasers are more commonly employed using 5-14 watts power (Beale and Gough, 2005).

This lack of standardisation of the technique has attracted criticism although it should be considered that lasers of 810-940nm wavelength all work in the same way. The light produced by these lasers is preferentially absorbed by haemoglobin (fig 1.5) and their principle mode of action is believed to be via secondary injury to the vein wall after superheating of blood within the lumen of the treated vessel (Proebstle, 2002b). Nevertheless it is also possible that direct vein wall injury is promoted by the laser fibre given that ablation is performed with the patient in the Trendelenburg position with the target vein compressed by surrounding tumescent anaesthetic.

More recently lasers of longer wavelength have become available and outcomes for a 1470nm laser have been published. At this wavelength energy is preferentially absorbed by water (fig 1.8) in the vein wall rather than by haemoglobin in erythrocytes. This, together with the use of a radial rather than bare tipped fibre has allowed a significant reduction in the power required to reliably achieve ablation of the target vein. Initial reports indicate that this has a major impact in reducing post-treatment discomfort without compromising efficacy (Pannier et al., 2009; Maurins et al. 2009).

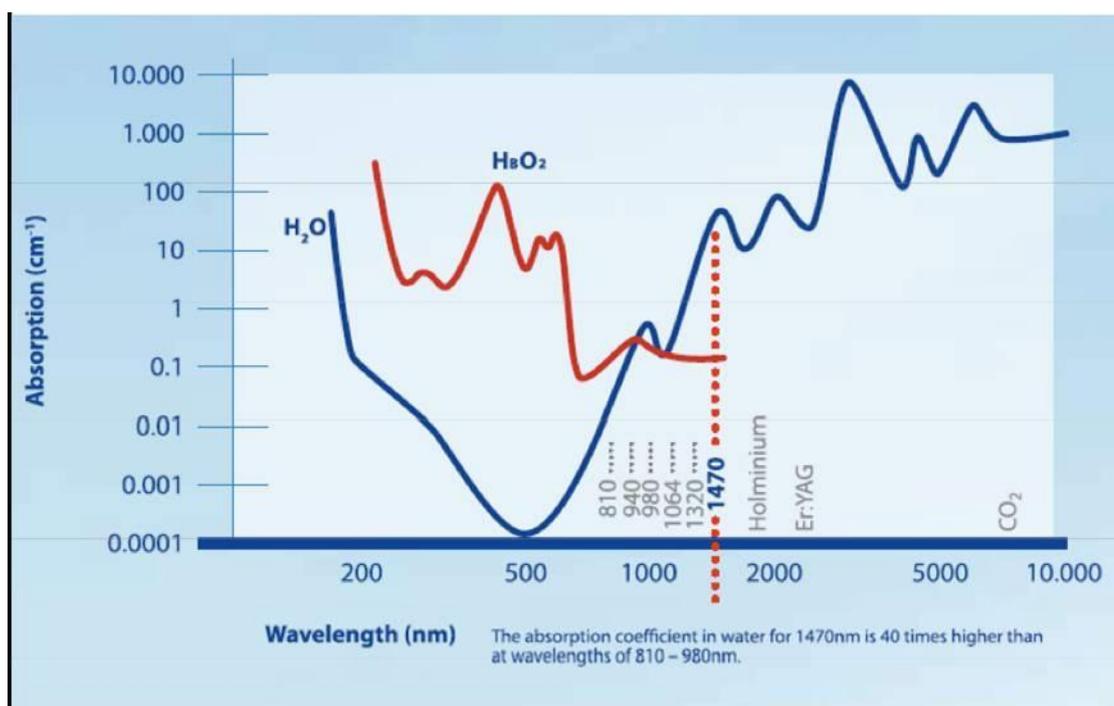


Figure 1.8: Absorption coefficient of laser energy at different wavelength by H₂O and HbO₂ (source: Boilitec AG, Jena, Germany)

A report by Min et al using an 810nm laser describes almost 500 patients followed for up to 3 years indicated GSV occlusion rates of 98% at 1 month and 93% at 2 years (n=121). No great saphenous veins regained patency after 2 years. The main complications were bruising (24%) and thrombophlebitis (5%) but there were no instances of DVT, burns or paraesthesia. A separate study reports one instance of temporary paraesthesia following GSV EVLA (Min et al., 2003).

Fear of possible nerve injury, a potential adverse effect of the high temperature at the tip of the laser fibre delayed the use of this technique for the treatment of SP/SSV reflux. However, the protective (heat-sink) effect of perivenous tumescent anaesthesia was reported by Beale et al in 2006 (Beale et al., 2006). Since then a number of studies have shown EVLA to be equally successful in treating varicosities that are secondary to this type of reflux.

The standard technique for EVLA (then called EVLT™) [endovenous laser treatment] as described by Min et al requires percutaneous insertion of the laser fibre into the GSV at knee level. It is advanced to the SFJ under ultrasound control. Peri-venous tumescent local anaesthetic (0.1% lignocaine) is infiltrated around the GSV throughout its length to provide analgesia, to compress the vein and thus promote close contact between the vein wall and the tip of the laser fibre, and to prevent thermal damage to surrounding tissues.

The laser fibre is fired as it is withdrawn from the truncal vein at a rate of 1cm/5sec at 12-14 watts power. This delivers around 70J/cm energy. Although some authors have also advocated applying manual pressure over the vein to further assist vein wall apposition this might increase the risk of vein wall perforation and bruising. Post-treatment compression in the form of bandaging or class II compression hosiery is worn for 1-2 weeks following treatment and patients are encouraged to resume normal activities as soon as they feel able.

To date there have been 5 randomised controlled trials comparing EVLA with conventional surgery. These suggest that abolition of reflux and improvements in quality of life are similar for both techniques. However EVLA appears to be associated with less post-treatment bruising and a more rapid return to normal activity. (de Medeiros et al., 2005; Ying et al., 2007; Beale et al., 2008; Rasmussen et al., 2008; Kalteis et al., 2008)

At present EVLA shows considerable promise although long-term follow-up and more rigorous evaluation of outcomes is awaited. These were also the conclusions of a systematic review of the published outcomes for EVLA (Mundy et al., 2005).

EVLA: How does it work?

Endovenous laser therapy causes thermal damage to the vein wall by the mechanisms described above. For those using a shorter wave-length (810-980nm) this results in focal coagulative necrosis, shrinkage and thrombotic occlusion of the vein (Proebstle et al., 2002b). Histological studies after *in-vitro* and *in-vivo* laser application have confirmed these findings together with instances of perforation, extravasation of blood around the vein, and a reduction in vein diameter 1 week following treatment [Weiss 2002; Proebstle et al., 2002b; Bush 2003]. Comparison of the histological results of VNUS Closure[®] and endovenous laser treatment found fewer vein wall perforations with VNUS Closure[®], which the authors claimed correlated with a lower incidence of haematoma (Weiss 2002). Interestingly however 2 recent studies, one of which was a randomised trial confirms that post-treatment pain and bruising is significantly reduced following ablation with a 1470nm diode laser compared to those of a shorter wavelength (Pannier et al 2010, Doganci & Demirkilic, 2010). Thus the putative advantages of this newer laser discussed earlier appear seem to be reflected in clinical practice.

EVLA: How effective?

Observational studies report GSV closure rates of 88-100% (Mundy et al., 2005) with an improvement in the appearance of superficial varicosities and relief of symptoms. Ablation of the GSV is considered to provide a similar haemodynamic effect to that of high tie and GSV stripping. Unlike surgery, individual varicosities are not necessarily treated initially (although some surgeons do perform concomitant phlebectomy) and any residual varicosities that remain 6 weeks or so after abolition of truncal vein reflux are typically treated by delayed sclerotherapy. Data from our own institution showed that some 40-50% of the patients require delayed sclerotherapy when EVLA is confined to the above-knee GSV but that this requirement is significantly reduced (17%) when ablation is performed to the lowest point of reflux (Chapter 5) or following SSV ablation (18%; Chapter 6).

A potential criticism of any minimally invasive technique that avoids SFJ ligation is that the GSV tributaries may remain patent. Ligation of these has previously been considered pivotal to reducing recurrence rates (Browse 1999). However Chandler et al have suggested that avoiding surgical disruption of the SFJ may reduce neovascularisation and thus recurrence rates may be lower (Chandler et al., 2000).

Complications of EVLA

Transient bruising and induration along the treated saphenous vein have been reported in 23-100% (Mundy et al. 2005) of patients with resolution within 3-4 weeks. Saphenous nerve paraesthesia has been documented in about 1% (Min et al., 2001; Proebstle et al, 2002 a) of limbs although this is usually temporary. Thrombophlebitis affects 3-8% (Proebstle et al, 2002 a; Min et al., 2003) of patients and may occur both in the treated vein and its tributaries. Deep vein thrombosis (DVT) is a rare (1%) complication following EVLA (Marsh et al., 2010). These complications appear less frequent with a longer wave-length (1470nm) laser (Pannier et al 2010, Doganci & Demirkilic, 2010).

Finally an unusual complication of EVLA is the development of an arteriovenous fistula. This has been reported in 4 patients (Timperman, 2004; Theivacumar and Gough, 2009; Ziporin et al., 2010). It is uncertain whether these are the result of thermal injury from the laser fibre or whether they are secondary to a “needle-stick” injury during administration of the tumescent anaesthesia.

1.8.5 Radiofrequency ablation (RFA)

Endovenous radio-frequency ablation (Closure system: VNUS® Medical Technologies Inc., Sunnyvale, CA) of the GSV was first described by Goldman (Goldman, 2000). Initially it was usually performed under general or regional anaesthesia and combined with phlebectomy. In some centres sapheno-femoral ligation was also undertaken. More recently local anaesthesia has been adopted by many surgeons. After cannulation of the GSV at knee-level a 5 or 8 French gauge catheter is advanced to the SFJ under ultrasound control and then slowly withdrawn. Heating of the vein and surrounding tissue results in endothelial denudation, collagen denaturation and acute vein constriction (Weiss, 2002). A multi-centre study found that 85% of GSV were obliterated at 2 years (Merchant et al., 2002), with other series reporting occlusion rates of 88-100% after similar follow-up (Manfrini et al., 2000 ; Rautio et al., 2002; Sybrandy et al., 2002). There have also been a number of RCTs examining the efficacy of RFA against conventional surgery which show that RFA is effective and, like EVLA, associated with a quicker post-treatment recovery (Lurie et al., 2005; Perälä et al., 2005; Luebke et al., 2008). However one study reported a DVT rate was up to 16% (Hingorani et al., 2004), the highest incidence following any endovenous ablation technique. This has not been substantiated by other studies.

Recently the manufacturers of the VNUS Closure device have introduced VNUS Closure Fast. Although this is also based on radiofrequency energy the mode of action is somewhat different relying on a heating coil (of 7cm length) rather than bipolar electrode technology. The putative advantages of VNUS Fast are that procedure times are quicker (and similar to those of EVLA) with less post-treatment discomfort than after EVLA (Almeida et al., 2009; Shepherd et al., 2010). Reported truncal vein ablation rates for VNUS Closure Fast is 99% which is generally superior to those for VNUS Closure (Proebstle et al., 2008). Nevertheless there is no comparative (RCT) data currently available for the newer device whilst a recent RCT comparing VNUS Closure with an 810nm diode laser has shown significantly better GSV ablation rates for the latter at 1 year (Gale et al., 2010).

Further, a meta-analysis of the outcomes for endovenous techniques for the treatment of varicose veins has indicated that successful GSV ablation is achieved significantly more often after EVLA than RFA (van den Bos et al., 2009) although the RFA data was derived from the results of studies for the original VNUS Closure device. These findings are summarised in figure 1.9.

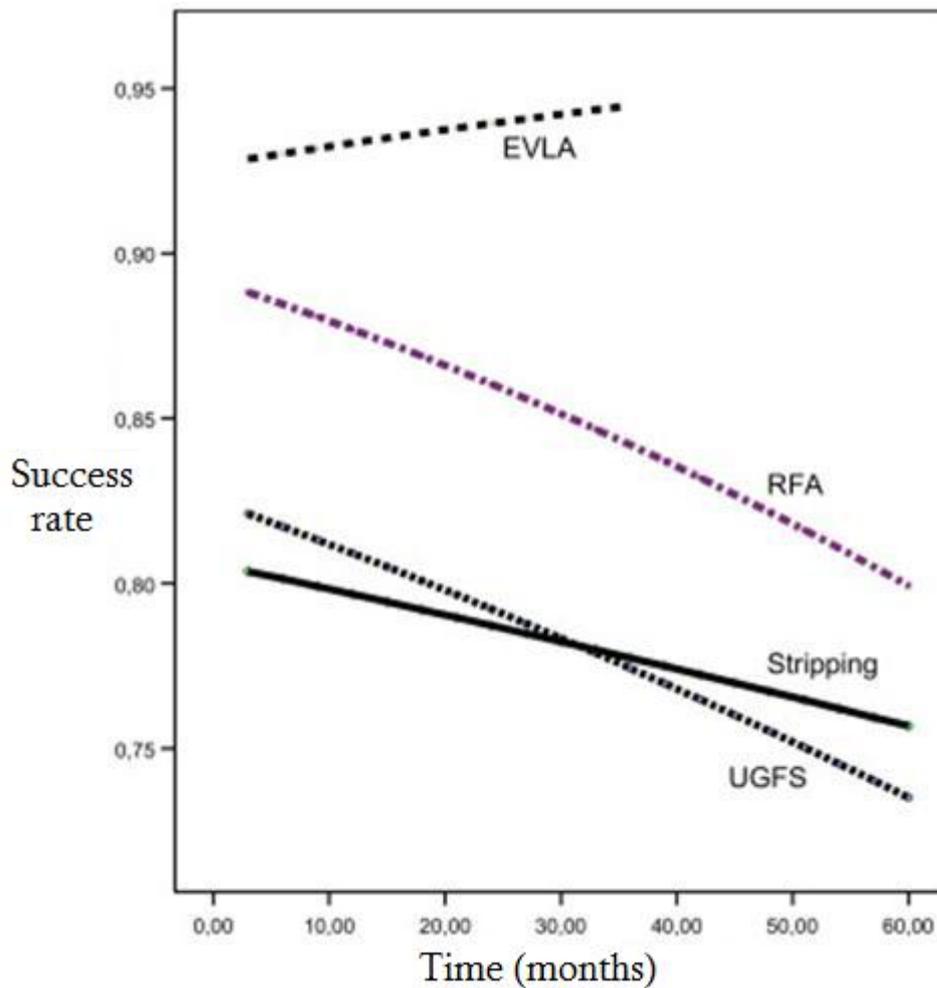


Figure 1.9: Anatomic success rate for different modalities of treatment

(Stripping: surgical stripping, UGFS: ultrasound guided foam sclerotherapy, EVLA: endovenous laser ablation, RFA: radiofrequency ablation (van den Bos, 2009))

1.8.6 Chemical Ablation (Sclerotherapy)

Sclerotherapy initiates a chemical thrombophlebitis that results in thrombotic occlusion of the target vein and subsequent vein fibrosis (chemical ablation) (Kern, 2002; Browse, 1999). Although sclerotherapy was introduced in the middle of the nineteenth century by Chassaignac (Browse, 1999), it was popularised by Fegan in 1960 (Fegan, 1960) with the introduction of an injection-compression technique. Interest in sclerotherapy diminished when Hobbs (Hobbs, 1968) published the results of a randomised study between sclerotherapy and surgery which showed a high failure rate following the former. Although various sclerosants [A: hypertonic solutions (hypertonic saline); B: emulsifying solutions (polidocanol, sodium tetradecyl sulphate (STD), ethanolamine oleate); C: corrosives (polyiodide iodine, chromated glycerine)] have been described (Browse et al., 1999), it would appear that sodium tetradecyl sulphate (STD) and polidocanol are most widely used (Partsch et al., 1997). STD is the only agent licensed for use in the UK.

The use of ultrasound in the diagnosis and assessment of venous disease was introduced in late 1980s. This in turn facilitated the concept of ultrasound guided sclerotherapy which was initially reported by Schadeck in 1991 (Schadeck and Allaert, 1991). Further, the idea of foam sclerotherapy originally described by Orbach (Orbach, 1950) using a “shaking method” was superseded by the two-syringe technique popularised by Tessari (Tessari, 2001). Although sclerotherapy was mainly reserved for isolated varicosities that were not associated with GSV (or SSV) reflux (Galland, 1998), there is a large variation in practice in different countries (Partsch, 1997). Foam sclerotherapy appears to be more effective than liquid sclerotherapy (Belcaro et al., 2003; Hamel-Desnos et al. 2003) and ultrasound guided foam sclerotherapy is now increasingly used to ablate both the GSV and SSV with success rates of 84-95% (Jia et al., 2007; Darvall et al., 2010). Although early truncal vein occlusion rates are acceptable recanalisation occurs in some 30-40% of treated veins within 2-3 years (Belcaro, 2003; Yamaki, 2004). This is reflected in the meta-analysis summarised in fig 1.6 (van den Bos, 2009).

Although the complications of sclerotherapy are generally minor (symptomatic thrombophlebitis, skin staining, ulceration, matting) (Jia et al., 2007) more serious adverse events have also been described including DVT, anaphylaxis, visual disturbance and stroke (Goldman, 2000; Frullini and Cavezzi, 2002). These serious complications occur more frequently with foam than after liquid sclerosant presumably because of its increased use in the GSV and the risk of the foam entering the femoral vein. If this occurs then a paradoxical embolus through a patent foramen ovale is possible thus accounting for the cerebral complications.

1.8.7 Surgical Treatment of Varicose veins

Surgical treatment aims to abolish truncal vein reflux and to remove visible varicosities (truncal vein stripping and multiple phlebectomies). Flush ligation of the superficial truncal vein to control the highest point of deep to superficial reflux is the basis of treatment. This remains the principal method of treatment offered to patients in the United Kingdom.

1.9 Complications of varicose vein treatments

Complications of varicose vein surgery are one of the commonest reasons for litigation, accounting for 17% of settled claims within the broad specialty of general surgery, including the highest Medical Defence Union (MDU) settlement for this specialty between 1990 and 1998 (MDU report, 2003). Cutaneous nerve injury is one of the commonest causes of litigation. It is often temporary but may be permanent in around 7% of patients (Holme et al., 1990). More disabling nerve injuries can also occur with at least 12 cases of foot drop being recorded on the NHS Litigation Authority database after sapheno-popliteal ligation. Published complication rates for all of the treatment modalities described in this chapter are summarised in table 1.6.

EVLA	<p>Bruising: 60-80% (Navarro et al., 2001; Min et al., 2001; Proebstle et al., 2002; Almeida et al., 2009)</p> <p>Saphenous nerve injury: <1% (Min et al., 2001; Bush, 2003)</p> <p>Hyperpigmentation: <4% (Proebstle et al., 2002)</p> <p>Thrombophlebitis: 3-8% (Mundy et al.,2005)</p> <p>DVT: 1% (Marsh et al. 2010)</p>
RFA	<p>Bruising: <35% (Puggioni et al., 2005; Almeida et al., 2009)</p> <p>*Saphenous nerve injury: 3-49%</p> <p>*Thrombophlebitis: 2–20%</p> <p>*Skin burns: 2–7%</p> <p>*(Manfrini et al., 2000; Merchant et al., 2002; Rautio et al., 2002; Sybrandy et al., 2002; Lurie et al., 2003)</p> <p>DVT: 1-16% (Hingorani et al., 2004; Marsh et al. 2010)</p> <p>Foot drop – 1 case reported (Kumar et al., 2010)</p>
Ultrasound-guided foam sclerotherapy (GSV)	<p>Transient visual disturbances: occasional (Frullini and Cavezzi , 2002; Forlee et al., 2006)</p> <p>Skin matting/staining/pigmentation: 8-55% (Kern,2002; Bountouroglou et al., 2006; Wright et al., 2006)</p> <p>Cutaneous neuro-sensory loss : <1% (Guex et al., 2005; Jia et al., 2007)</p> <p>Thrombophlebitis:4-10% (Kern,2002; Bountouroglou et al., 2006)</p> <p>DVT: <1% (Kern,2002; Wright et al., 2006; Bountouroglou et al., 2006)</p>
Surgery (Sapheno-femoral ligation &GSV stripping to knee)	<p>Haematoma: up to 10% (Corder et al., 1991)</p> <p>Cutaneous neurosensory loss : 5-7% (Holme et al., 1990)</p> <p>Wound infection: 2–15% (Corder et al., 1991)</p> <p>DVT : <1% (Critchley et al., 1997)</p>

Table 1.6: Complication rates following different methods of treatment for GSV incompetence

1.10 Recurrence rates following varicose vein treatment

Although the RCTs of surgery and the newer endovenous therapies have shown that outcomes are similar in the short term it is also apparent that medium term follow-up of patients after surgery show that 25-37% of patients develop further varicose veins after 2-5 years (Munn et al., 1981; Dwerryhouse et al., 1999). Further, late results suggest that recurrence occurs in the majority (>60%) after ≥ 10 years (Campbell et al., 2003, Winterborn et al. 2004a). Recurrence after surgery may be related to technical factors and in particular appear higher after sapheno-femoral ligation without GSV stripping (Sarin et al. 1994, Jones et al. 1996). Further, Egan et al. (Egan et al., 2006) concluded that incomplete surgery was responsible for up to 80% of recurrences (17% intact GSV, 37% stump reflux, 44% incompetent thigh GSV) in a series of 500 patients undergoing surgery for recurrent varicose veins following previous surgery for GSV-related varicosities. Similarly van Rij et al. (2003) reported recurrence rates of 50% 3 years following SPJ ligation. It is likely that this reflects both the lower rate of truncal vein stripping (fear of sural nerve injury) and the failure to perform a technically satisfactory sapheno-popliteal ligation due to the variable position of the junction in patients with small saphenous vein varicosities.

Despite these publications many believe that the principle cause of recurrence following surgery is neovascularisation at the site of junctional ligation (Blomgren et al. 2005, de Maeseneer et al. 2007) and Winterborn et al (2004a) showed that its incidence increased sequentially during follow-up (36%, 54%, 65% at 2, 5, 11 yr). The mechanisms by which this phenomenon occurs will not be discussed further here.

Overall some 20% of the patients requiring treatment for varicose veins do so because of recurrence (Darke, 1992; Ruckley, 1997). Although the causes of recurrence include incompetent perforators, para-reflux, new sites of reflux and inadequate primary surgery, neo-vascularisation is thought to be the commonest cause for recurrence (Jones

et al., 1996). Histological evidence suggests that this is the result of angiogenesis at the site of truncal vein ligation (Nyamekye et al., 1998) although attempts to reduce this by technical modifications to the surgical technique (closing the cribriform fascia, oversewing the SFJ stump, interposition of a PTFE patch) are of unproven benefit (Earnshaw et al., 1998; Frings et al., 2004).

Although the data on recurrence rates may appear confusing this largely reflects the different lengths of follow up and the definition of recurrence. Table 1.7 summarises the data reported in various studies for Duplex ultrasound detected and clinical recurrence after conventional surgery for varicose veins.

Currently, the long term recurrence rates after minimally invasive therapies are unknown. Nevertheless since truncal vein ablation is performed under ultrasound control it is probable that “technically inadequate surgery” is less likely to be a factor in this. Work presented in this thesis will examine the possible impact of neovascularisation on the risk of recurrence following EVLA. In addition, the influence of “non-ligated tributaries” at the sapheno-femoral junction on recurrence will also be explored.

	Duplex	Clinical	Re-treatment rates
Surgery (Sapheno femoral ligation and GSV stripping)	15% [1yr] (Turton et al., 1993) 13% [2yrs] (Jones et al., 1996) 29% [5yrs] (Dwerryhouse et al., 1999) 62-70% [10 -11years] (Campbell et al., 2003; Winterborn et al., 2004)	25% [2yrs] (Jones et al., 1996) 37% [3yrs] (Munn et al., 1981) 21% [5yrs] (Dwerryhouse et al., 1999)	6% [2yrs] (Jones et al., 1996)
Ultrasound guided GSV foam sclerotherapy	27% [1yr] 64% [5yrs] (Chapman-Smith and Browne, 2009)	4% [10yrs] (Chapman-Smith and Browne, 2009)	9% [1 yr] (Darvall et al., 2010)
Radiofrequency ablation (VNUS®)	10% [9mths] (Rautio et al., 2002)	5% [6mths] (Dauplaise and Weiss, 2001) 3.8% [1yr] (Sybrandy and Wittens, 2002) 14% [2yrs] (Whiteley et al., 2000)	Not known
Endovenous laser ablation (EVLA)	1-2% [6mths] (Min et al., 2001) <7% [3yrs] (Min et al., 2003)	Not known	Not known

Table 1.7: Recurrence rates after treatment for varicose veins

Chapter 2:

2. General Methodology

2.1 Assessment of patients with varicose veins

All patients attending the venous clinic at The General Infirmary at Leeds between March 2005 and May 2007 were assessed (clinically and by using DUS) and provided that informed consent was obtained they were recruited for the studies that are presented in this thesis. This chapter describes the general methodology whilst methods for individual studies are described in each chapter.

2.2 Clinical assessment

Clinical History

All patients were assessed clinically to identify symptoms and signs related to venous disease both before treatment and at every follow up visit. Relevant history including the duration of symptoms, the nature of these (aching, itching, heaviness of leg, ankle swelling), a previous history of superficial thrombophlebitis, deep vein thrombosis (DVT) or major limb trauma, and usage of anticoagulants (warfarin) or antiplatelet drugs (aspirin, clopidigrel) were recorded. Family history of varicosities and previous treatment details were also documented.

Severity assessments

The clinical severity of venous disease was established using CEAP [Clinical, etiology, anatomy and pathology] (Porter and Moneta, 1995) and Venous Clinical Severity Score (VCSS, Rutherford et al., 2000). Further the impact of disease specific quality of life was determined using the Aberdeen Varicose Vein Severity Score [AVVS] (Garratt et al., 1993). The questionnaire is reproduced in appendix B3.

The AVVS questionnaire is a 13-item disease-specific health-related quality of life measure for people with varicose veins. The questions cover both symptoms and the cosmetic impact of varicose veins and includes a diagram on which patients indicate the distribution of their varicosities. It was developed by Garratt and colleagues in 1993 and has been shown to have validity, reliability and reproducibility (Garratt et al., 1993; Smith et al., 1999). It has also been shown to be responsive to change and an improvement in AVVS has previously been demonstrated in patients following varicose vein surgery (Garratt et al., 1993; Smith et al., 1999; Mackenzie et al., 2002). Questionnaires were completed before and at 6, 12 and 52 weeks following treatment.

Changes in symptoms and signs, together with treatment-related complications and the presence of residual or recurrent varicosities were recorded at each post-treatment clinic visit together with any additional intervention that was required.

Pain severity, patients' satisfaction and willingness to undergo the same treatment again were recorded in specific studies and these methods are described in the relevant chapters.

2.3 Duplex ultrasound assessment

All patients underwent routine DUS assessment according to the consensus document published by Coleridge-Smith et al (Coleridge-Smith et al., 2006; Cavezzi et al., 2006) using a portable TITAN ultrasound machine (TITAN®, Sonosite Inc, Bothell, USA) and a 5-10MHz probe both before and after treatment. The superficial, deep and perforating veins were assessed to identify all incompetent (or occluded) veins. The presence of retrograde flow lasting >1s was considered significant.

DUS examination was usually carried out with the patient standing and the distal calf muscle was compressed manually and released abruptly for assessment of reflux. However, examination of distal calf veins was performed with the patient sitting and foot compression was used to augment flow. Transverse and longitudinal views of the relevant veins, saphenous junctions and perforating veins were employed to identify the anatomy and presence of reflux more precisely.

An angle of insonation of 45-60° between the transducer and vein was used to achieve optimum colour or Doppler spectral signals. Patients with reflux in the superficial truncal veins associated with incompetent saphenous junctions were assessed for laser suitability and the criteria for this are given below.

After treatment reflux at the saphenous junctions and the ablation status of the target truncal vein were recorded for all patients. Compressibility and detectable flow in the treated vein was considered ablation failure whilst absence of flow in a non-compressible vein represented successful ablation. SFJ tributaries and the patency and reflux status of the below-knee GSV (BK-GSV) were assessed in detail for specific studies and these methods are described later.

2.4 Training received

Duplex ultrasound scanning skills were initially gained by attending an introductory course at Kings College, London followed by 6 months (from March 2005-Sep 2005) hands-on training by a senior ultrasonographer at the General Infirmary at Leeds. Data collection for most studies described in this thesis was dependent on DUS findings and thus the reliability of the information obtained has been assessed in two ways:

1. Consecutive varicose vein patients attending the venous clinic during a two-month period were scanned by the writer using the TITAN ® scanner and by a senior ultrasonographer with a Philips ® (iU22) ultrasound scanner (Andover, MA). Twenty-four limbs were studied. The accuracy was 100% in detecting reflux in the deep & superficial veins.

2. The tributaries of the GSV at the SFJ were scanned and documented for comparison with the operative findings. Site marking of the perforating veins was also compared with operative findings. Identifying groin tributaries ($\geq 2\text{mm}$) that require ligation was accurate in 88% patients and perforator localisations ($\pm 1\text{cm}$) in 96% patients.

Hands-on EVLA training was received between May–September 2005 from the two senior consultant vascular surgeons (Professor MJ Gough and Mr AID Mavor) who, at that time, had the largest experience of EVLA in the UK. Experience in the treatment of residual varicose veins by foam sclerotherapy was also gained from these consultants.

2.5 Suitability for standard EVLA

Suitability for EVLA depended upon a $\geq 10\text{cm}$ relatively straight segment of GSV (or SSV, AAGSV in the appropriate studies) immediately distal to the SFJ / SPJ, an absence of significant varicosities arising within 10cm of the SFJ, and a GSV diameter of $\geq 3\text{ mm}$ at the intended site of cannulation (usually just above the knee). The main patterns of varicosities that are and are not suitable for EVLA are illustrated in figures 2.3 and 2.4. The presence of two incompetent truncal vein joining at the SFJ did not preclude EVLA although these patients may only have been suitable for inclusion in some of the studies.

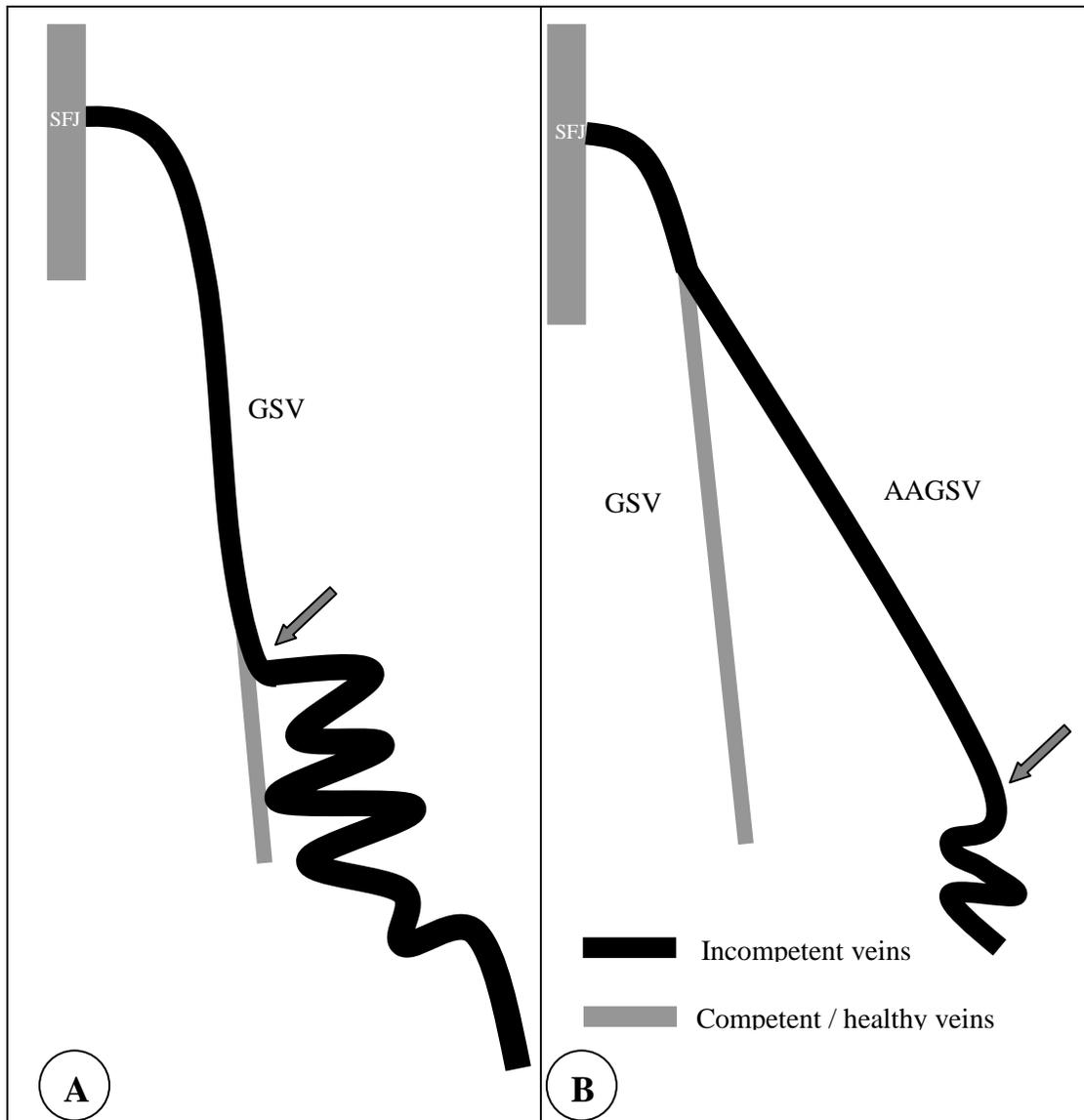


Figure 2.1: Illustrations showing varicose veins that are suitable for EVLA

A- Adequate (>10cm) length of truncal vein (GSV) is present before varicosities join

B- GSV tributaries (anterior accessory great saphenous vein (AAGSV) in this example) are usually relatively straight before becoming varicose

Arrows indicate suitable cannulation sites

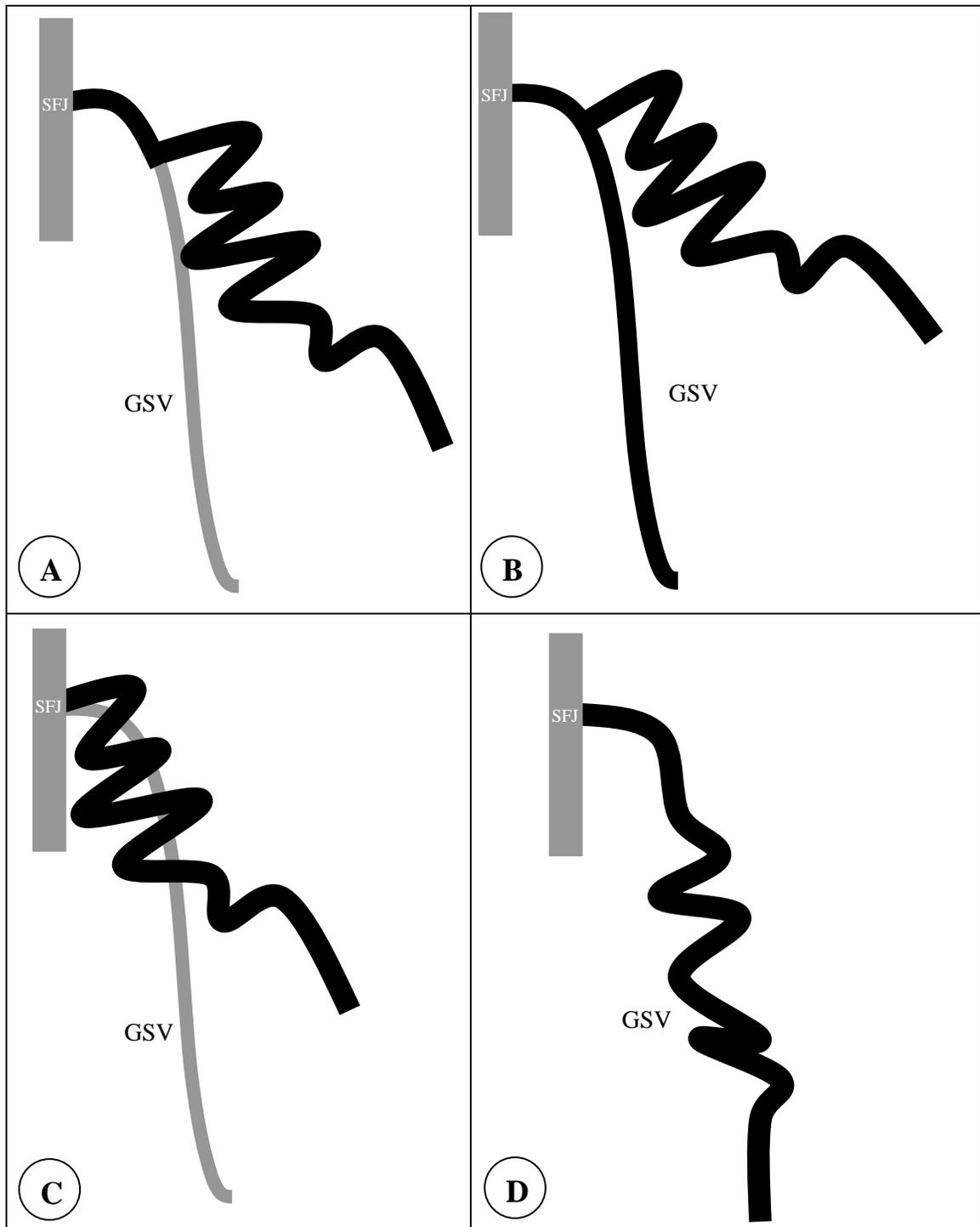


Figure 2.2: Illustration showing some patterns of varicose veins that are not suitable for EVLA

- A- Only a short segment of truncal vein reflux
- B- Varicosities arising within a short distance of SFJ
- C- No truncal vein reflux, varicosities arising directly from SFJ
- D- Excessive GSV tortuosity

2.6 Patient selection

Patients attending the venous clinic at The General Infirmary at Leeds were assessed clinically and by DUS in the outpatient clinic. Suitability for laser treatment was assessed and EVLA was offered as an alternative to surgery in appropriate patients. If suitable, patients were asked to take part in various clinical studies. Further, a prospective database was maintained of all patients undergoing EVLA. Two studies, namely “factors influencing effectiveness of EVLA” and “the reliability of a scoring system to assess the outcome of EVLA” were performed using information from this database.

2.7 Pre-procedure preparations

Patients were treated on an out-patient basis, initially in the surgical day unit but subsequently in a treatment room in the out-patient clinic. Written informed consent was obtained for both the procedure itself and for participation in any study for which consent had been given. All studies included in this thesis had the approval of the Leeds Teaching Hospitals NHS Trust Research Ethics Committee. Immediately prior to treatment a detailed DUS was repeated to identify and mark the truncal vein (GSV, SSV, or AAGSV) for treatment. When necessary, more than one truncal vein/limb was treated at a single visit. Similarly in patients with bilateral varicose veins both legs were usually treated on the same occasion.

Any other variables that were recorded are described in the methodology for the individual studies.

2.8 The standard technique for EVLA

Equipments

The following equipment was used for EVLA:

- i. Seldinger needle, 5F
- ii. Double ended J/straight 120cm 0.035” guidewire
- iii. 70cm 5Fr sheath
- iv. Laser fibre, bare tipped, 600micron
- v. 810 nm diode laser power source (Boilitec AG, Jena, Germany)

All the above were supplied by Synergyhealth® (EVLA Accessory pack 19042, Synergyhealth®, Chorley, UK). In selected patients when the truncal vein for treatment was particularly tortuous, or if the standard guidewire could not be passed along the full length of the vein for treatment a 0.035” J-tipped hydrophilic guidewire was used (Terumo Glidewire®, Terumo Medical Corporation, Somerset, USA).

Other disposables

- i. 10ml, 20ml syringes
- ii. 3-way tap
- iii. 25G needle
- iv. 20G (152cm long) Spinal needle
- v. 0.9% saline
- vi. 2% lignocaine with adrenaline for dermal local anaesthesia
- vii. Tumescant local anaesthetic solution (20 ml of 2% lignocaine with adrenaline 1:1000 mixed with 480 ml of 0.9% saline)

- viii. ultrasound probe cover
- ix. plastic receiver dish
- x. galipot
- xi. sterile swabs

Summary of technique for EVLA

The GSV was cannulated (using ultrasound guidance) at the level of knee or higher if there was only a relatively short straight segment of GSV. A guidewire was introduced proximally into the GSV & femoral vein and a 5FG catheter was positioned 1cm distal to the sapheno-femoral junction (SFJ) under ultrasound control. Perivenous tumescent local anaesthesia (0.1% lignocaine 150-200ml) was infiltrated along the vein using ultrasound guidance. This provided anaesthesia, compressed the GSV, absorbed the heat generated by the laser, and separated surrounding tissues from the vein. A laser fibre connected to an 810 nm diode laser source was inserted through the catheter and then both were withdrawn so that 4-5 pulses of laser energy (12Watts power, 1 second pulses, 1 second intervals) were delivered to each cm of vein (48-60 Joules/cm).

Following treatment a non-stretch compression bandage was applied from foot to groin for one week followed by a class 2 support stocking for a further week. Patients were prescribed 50 mg diclofenac sodium three times a day for 3 days to reduce inflammatory changes in the treated vein and encouraged to resume their normal daily activities (including work) as soon as possible.

If required, residual varicosities were treated by foam sclerotherapy (sodium tetradecyl sulphate) 6 weeks following initial treatment.

2.9 Detailed description of technique

On-table preparation

For GSV ablation the patient was positioned on a tilting table with the leg to be treated slightly flexed at the knee and hip with the latter externally rotated. The patient lies prone for SSV treatment. The table is tilted into the reverse Trendelenburg position to fill the lower limb veins.

After preparing the limb with povidone iodine a sterile towel was placed beneath it. Under ultrasound guidance, the vein was cannulated percutaneously after anaesthetising the overlying skin (1% lignocaine).

Cannulation Techniques

A 5 Fr needle connected to 10 cc syringe containing 5 ml of normal saline (0.9% NaCl) was used with the target vein imaged (DUS) transversely (Figure 2.5).

The target site for cannulation was positioned in the middle of the screen and local anaesthetic (lignocaine 1%, 0.5 ml) injected 2-3cm distal to the probe in line with the vein. The vein was imaged proximally for 5cm to determine its direction. The needle was inserted towards the vein under ultrasound guidance. The needle tip was initially positioned just above the vein and then advanced into the vein. Aspiration of blood into the syringe confirmed the intravenous position of the needle. While stabilising the needle in the same position, the syringe was disconnected and a 4Fr, J-tipped guidewire inserted into the vein through the needle.

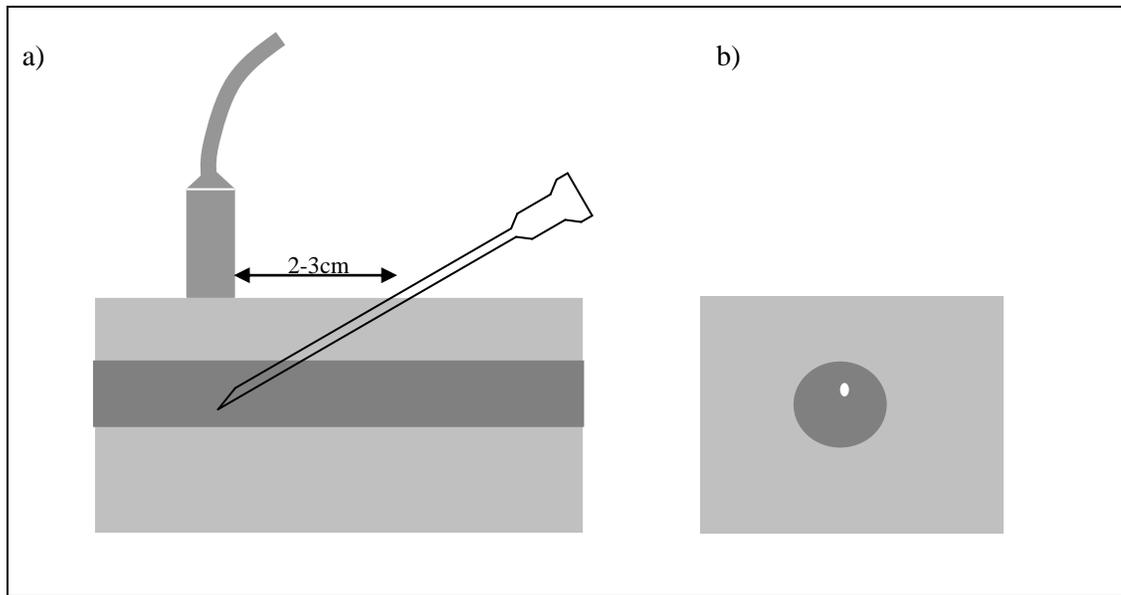


Figure 2.3: a) Cannulation of a vein under transverse ultrasound guidance. The skin is punctured 2-3cm distal to the ultrasound probe and vein puncture site. b) Representation of ultrasound appearance; the white dot within the vein is the tip of the needle.

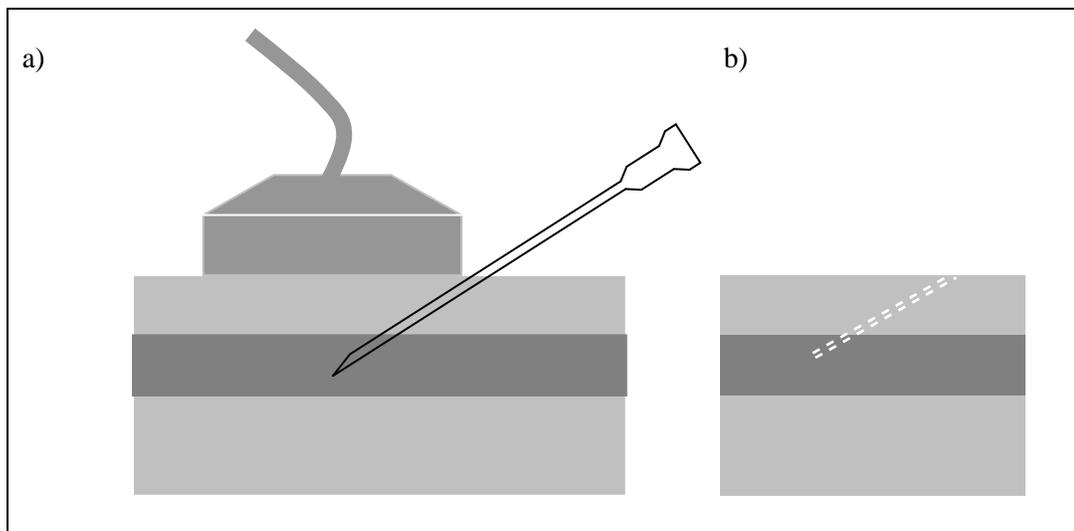


Figure 2.4: a) Cannulation of a vein using longitudinal ultrasound imaging. Note that the skin is punctured just distal to the ultrasound probe: b) Representation of ultrasound appearance; the white lines indicate the walls of the needle.

The other commonly used technique was to image the target segment of vein longitudinally and puncture the skin under local anaesthesia at the distal end of the probe (Figure 2.6). If the target vein was superficial it was sometimes useful to access the vein with a 16G intravenous catheter using a longitudinal view of the vein. The advantage of this technique is that the “flush-back” seen at the end of the catheter helps to prevent penetration of the back wall of the vein.

Overcoming problems with cannulation

Occasionally cannulation under ultrasound control was not possible. When this was the case then administration of a further aliquot of local anaesthetic into the subcutaneous tissues facilitated a small stab incision following which the target vein was delivered through the wound using a phlebectomy hook. This then allowed the operator to make a small venotomy and insert the guidewire under direct vision.

Further problems may occasionally be experienced when passing the guidewire up the vein, particularly if it was tortuous. Most difficulties were overcome by using a hydrophilic coated guidewire with an angled tip (Terumo Glidewire®, Terumo Medical Corporation, Somerset, USA). This was generally introduced via the endovenous sheath if the standard guidewire had passed partly up the vein.

The endovenous sheath

A 5 Fr single lumen sheath of either 45cm or 70cm length (standard technique) was used. The sheath is marked at 1cm intervals to facilitate accurate withdrawal for optimum laser energy delivery (Figure 2.7).



Figure 2.5: A 70cm length endovenous sheath marked at 1cm intervals

The sheath was inserted over the guidewire and its tip positioned 1cm distal to the SFJ. When positioning the tip of the catheter, if not clearly visible on ultrasound, saline was injected through it and the jet emanating from the tip was easily identified with ultrasound. The length of the vein to be treated was recorded using the scale on the sheath.

Tumescent anaesthesia (TA)

Tumescent anaesthesia (lignocaine 0.1% [20 ml 2% lignocaine with 1:1000 adrenaline mixed with 480ml normal saline]) was administered along the target vein under ultrasound guidance. The main purpose of the tumescent anaesthesia was to separate the vein from adjacent tissues and thus prevent inadvertent thermal damage to nerves and skin. The other purposes of the tumescent anaesthesia (TA) are summarised in table 2.1.

Function of tumescent anaesthesia	Explanations
Protects surrounding tissues (nerve, skin) from thermal injury	Absorption of heat by the fluid around the vein
Results in superior ablation rates	TA compresses the target vein around the laser fibre and reduces the distance between vein wall and laser tip; it also reduces the amount of blood inside the vein and thus thrombus formation.
Provides analgesia	It reduces intra-procedure pain by absorption of heat and by its local anaesthetic effect.

Table 2.1: Functions of tumescent anaesthesia

Technique for administration of tumescent anaesthesia

TA was administered using 15cm long spinal needle under ultrasound guidance. After insertion of the sheath, the target vein usually vasoconstricts. The sheath itself is visualised as two white dots (the anterior and posterior walls of the sheath) on ultrasound. Keeping the two dots (cannulated vein) in the middle of the screen, the spinal needle connected to 20cc syringe was inserted 2-3cm from the probe after anaesthetising the skin with 1% lignocaine and advanced towards the vein. The needle tip was positioned deep to the saphenous fascia and superficial to the anterior wall of the vein (figures 2.8 & 2.9). An adequate amount of TA was injected until a 0.5-1cm radius of TA

surrounded the target vein to achieve the typical “doughnut” appearance on ultrasound (figure 2.10). The needle is advanced proximally to deliver TA along the whole length of the vein requiring treatment with additional administration of local anaesthetic to the skin every 15cm or so. It is also important to inject adequate TA at both the SFJ and SPJ beyond the tip of the sheath. It is also crucial to administer adequate TA anterior to the vein to prevent skin burns in very superficial veins and to have adequate TA posterior to the vein particularly at the SF and SP junctions to protect the femoral and popliteal veins.

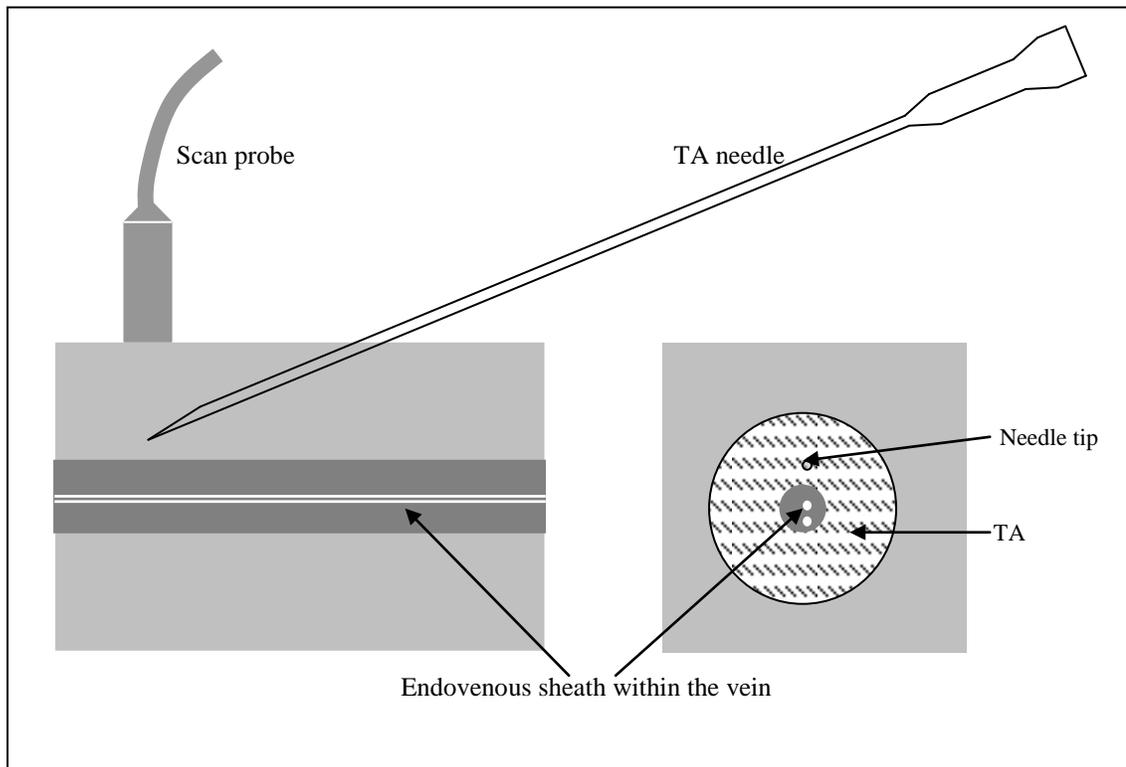


Figure 2.6: Technique for infiltration of tumescent anaesthesia: transverse view (left) shows the dough-nut appearance following administration

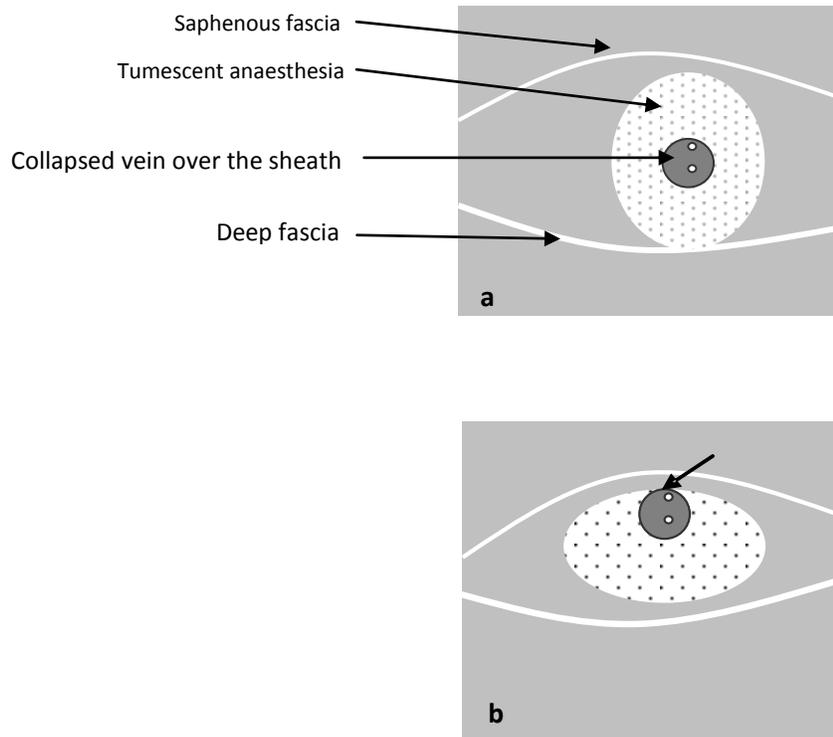


Figure 2.7: a) adequate tumescent anaesthesia around the vein: b) Insufficient TA anterior to vein (arrow)

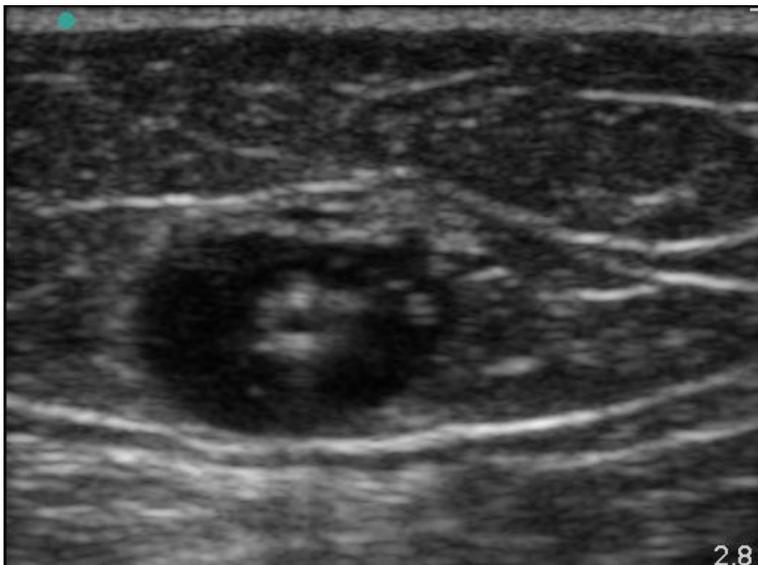


Figure 2.8: Ultrasound image showing “doughnut” appearance of TA

Delivery of laser energy

The bare tipped laser fibre was inserted into the endovenous sheath and advanced to the tip of the sheath (a mark on the laser fibre indicates the length for insertion) and the latter was then withdrawn by 1cm to position the tip of the laser fibre in the same place as the sheath was previously located, but with 1cm of the fibre extending beyond the sheath. The laser fibre was subsequently connected to the power source (figures 2.11 & 2.12) that delivered laser energy at 12W power with 1s laser pulses at 1s interval. Both laser fibre and the endovenous sheath are withdrawn together (locked together by a luer-lock system) whilst pulses of laser energy are delivered to the target vein. In the standard technique 4-5 laser pulses at 12W power were delivered per cm of vein as recommended by the manufactures (energy density: 48-60J/cm).

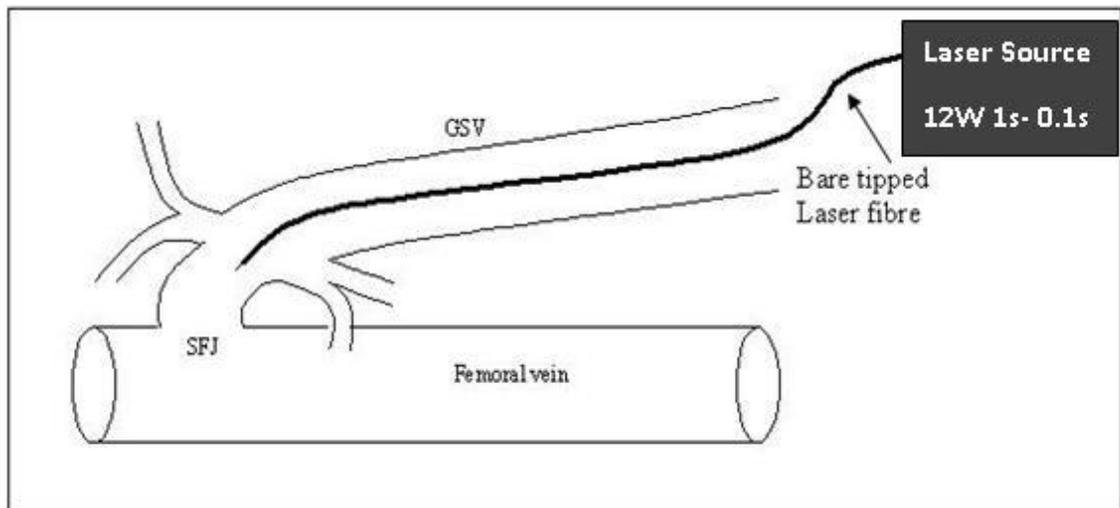


Figure 2.9: Bare-tipped laser fibre connected to laser power source



Figure 2.10: 810nm diode laser power source set at 12W and 1s pulses with a 0.1s interval

Completion of laser treatment

On completion of treatment a steristrip was applied to the cannulation site. A Panelast® (Panelast, Lohmann-Rauscher, Austria) bandage was then applied from foot to groin but with a strip of foam laid over the treated vein to apply compression for 1 week. This was then replaced with a Grade 2 compression stocking (Mediven stocking, medi-UK, Hereford, UK) which was worn during the day for the second week.

It should be noted that since the studies that are described in this thesis were performed patients now wear a Class 2 compression stocking from the time of treatment (continuously for the first week) and that the foam strip is no longer used.

2.10 Post treatment

Instructions

Patients were advised to resume their normal activities, including work, as soon as possible. Diclofenac sodium 50 mg three time a day was prescribed for 3 days (unless there were contraindications to this: peptic ulcer, oesophagitis, asthma) to reduce post-laser discomfort. Patients were routinely reviewed at 6 and 12 weeks and any residual varicosities treated with foam sclerotherapy if requested.

Follow up assessments

All patients were seen at 6, 12 and 52 weeks following treatment and all limbs were assessed clinically and by using DUS. A prospective log of complications was maintained. Nerve damage (sensory) was assessed objectively using a Neurotip (Owen Mumford Ltd, Woodstock, England) on patients who reported subjective numbness.

If residual varicosities were present at the 6 week follow up visit they were treated with 1-3% STD foam sclerotherapy (if requested by the patient). Foam was prepared according to the Tessari method (Tessari et al., 2000) and sclerotherapy performed using either a 25G hypodermic needle or butterfly needle (Abbott, Maidenhead, UK). A compression bandage (Panelast®) was applied with local re-enforcement using cotton wool balls over the treated vein. This compression bandage was left in-situ for 1 week and patient advised to walk 2-3 mile per day. Patients were followed up after a further 6 weeks to reassess the legs. Any complications were documented and further sclerotherapy was given if required.

Summary of follow up schedule

As indicated above patients were reviewed at 6, 12 and 52 weeks unless stated otherwise in individual studies. All patients were assessed clinically for residual or recurrent veins and for

improvements in symptomatology. This was assessed both verbally and objectively using the methods described in Table 2.2. Data analysis and statistical methods for each study are described in the individual chapters.

	Pre-op	6 weeks	3 months	1 year
Clinical assessment	✓	✓	✓	✓
Duplex ultrasound scan	✓	✓	✓	✓
AVVS	✓	✓	✓	✓
CEAP	✓		✓	✓
VCSS	✓		✓	✓
Requirement for injection sclerotherapy		✓	✓	✓
Satisfaction (VAS)			✓	✓
Complications		✓	✓	✓

Table 2.2: Summary of follow-up protocol

AVVS: Aberdeen varicose vein severity score

VCSS: Venous clinical severity score

CEAP: clinical sign, etiology, anatomy, pathophysiology

VAS: visual analogue scale

Chapter 3:

3. Factors influencing the effectiveness of EVLA

Successful ablation of the target truncal vein could be influenced by several factors. Two studies were conducted to analyse these factors.

3.1 Study 1: Technical Factors influencing the effectiveness of EVLA

3.1.1 Introduction

A successful long-term outcome depends upon elimination of the highest point of “deep to superficial” incompetence and ablation of the incompetent truncal vein. (Trendelenburg, 1891; Rivlin, 1975; Tibbs and Fletcher, 1983; Koyano and Sakaguchi, 1988; Corbett et al., 1988; Goren and Yellin, 1991). This chapter examines factors that might determine the efficacy of EVLA using data derived from patients undergoing treatment for GSV incompetence and SFJ reflux. Successful ablation of the treated vein is crucial in determining the long-term success of EVLA and a previous meta-analysis indicates that this is achieved in 88-100% of limbs (Mundy et al., 2005).

Similar success rates are reported for radiofrequency ablation [RFA] (Manfrini et al., 2000; Merchant et al., 2002; Rautio et al., 2002; Sybrandy and Wittens, 2002), although the potential mechanisms of injury may be different for the two techniques. RFA (VNUS Closure) delivers thermal energy to the GSV resulting in controlled heating to 85⁰C for a set period of time. This is a lower temperature than that achieved by EVLA but it is maintained for longer. It is believed that RFA causes endothelial denudation, collagen denaturation and acute vein constriction (Weiss, 2002). Whilst RFA relies on a standard protocol for the treatment of all patients this is not the case for EVLA. The power of the laser, the total energy delivery and the amount of energy delivered/cm

of vein (energy density) are all under the control of the operator. Nevertheless when EVLA was first introduced into clinical practice the manufacturer (Diomed Inc, Andover, MA) advised the use of 12W power delivering around 48J/cm vein. However, since not all studies report 100% occlusion rates success may depend on a number of factors. These have been examined in this observational study with the aim of developing a standardised protocol to ensure successful ablation in as many patients as possible.

3.1.2 Methods

Patients

All patients attending the venous clinics at the General Infirmary at Leeds and the BUPA Hospital, Leeds between January 2002-April 2006 with SFJ and GSV reflux were evaluated by duplex ultrasound scanning to assess their suitability for EVLA. If appropriate, this was offered as an alternative to surgery and patients were treated according to their preference. Those who required ablation of an additional truncal vein (anterior accessory saphenous vein or SSV) or who were taking warfarin were excluded from the study. (Of the 582 patients included in this study, 312 patients' data was collected by my predecessor Rosie Beale and the remaining data is collected by me).

EVLA suitability

Suitability for EVLA depended upon a ≥ 10 cm relatively straight segment of GSV immediately distal to the SFJ, an absence of significant varicosities arising within 10cm of the SFJ, and a GSV diameter of ≥ 3 mm at the intended cannulation site (usually just above the knee).

Standard laser technique

This was described in Chapter 2. A bare-tipped laser fibre connected to an 810 nm diode laser source (Diomed Inc, Andover, MA) was used to deliver 4-5 pulses of laser energy (12W power, 1s

pulses, 0.1s intervals) per cm vein. Neither concomitant phlebectomy nor foam sclerotherapy was performed at the time of primary treatment. Post-EVLA care was as described in Chapter 2.

Follow-up

Patients were reviewed at 6 and 12 weeks. Treated limbs were assessed clinically and by duplex ultrasound scanning. Those who had residual varicosities with controlled truncal reflux (occluded GSV) were offered foam sclerotherapy (as per Chapter 2) at the 6 week visit. Patients with persisting significant GSV reflux (>1s) at any follow-up appointment were offered the choice of conventional surgery or repeat EVLA.

Criteria for successful GSV ablation on ultrasound were non-compressibility or non-visualisation of the treated segment of vein together with an absence of flow on colour-flow duplex ultrasound and a competent SFJ. Treatment failures were defined as veins demonstrating flow and/or reflux in all or part of the treated segment of the GSV.

Data collection and analysis

The following data were collected and stored on a prospectively maintained database (Microsoft Office Access, 2003) by 3 research fellows and 2 consultant vascular surgeons trained in venous duplex ultrasound:

- Patient height and weight (without footwear) and calculated body mass index (BMI).
- Maximum GSV diameter on ultrasound (avoiding focal dilatations) whilst standing.
- Length (L) of GSV treated.
- The total laser energy (TLE) delivered to the GSV (obtained [Joules] from laser power source)
- The energy density (ED, J/cm) administered: TLE/L.

- Data on whether the GSV had been successfully ablated (see above) either throughout the “treated” length or partially if this was applicable.

A prospective log of all complications that occurred after EVLA was also maintained.

Examination of the database identified two groups of patients:

- a) Those with full-length occlusion of the treated GSV and a competent SFJ (Group A)
- b) Those with a fully or partially patent GSV, irrespective of any clinical improvement or the reflux status of the SFJ (Group B).

Statistical analysis

Variables between the two groups were compared using a student-t test (unpaired) and a chi-square test employed to compare complication rates between the groups. A “p” value of <0.05 was considered statistically significant. Data are presented as median (\pm inter-quartile range) unless stated otherwise. All analysis were performed using the statistical package SPSS® for Windows (SPSS (14), Chicago, Illinois, USA).

3.1.3 Results

582 patients (644 legs) were reviewed at 6 weeks and 3 months. Demographic data, including the severity of the venous disease (C of CEAP) are shown in Table 3.1. In 599/644 (93%) the 3-month ultrasound scan confirmed full-length ablation of the treated GSV. Of the remainder the GSV was partially occluded in 19/644 (2.9%) legs and patent in 26/644 (4%). The median energy density delivered during ablation was 48 (\pm (IQR 37-59) J/cm in group A and 37 (\pm (IQR 30-46) J/cm in group B. This difference was statistically significant ($p<0.01$). There was also a difference in the total laser energy used (Group A: 1877J versus Group B: 1191J, $P<0.05$) although this is not reflected by a difference in the median length of GSV treated in the two groups (Group A: 33cm

versus Group B: 29cm). The median GSV diameter was similar in the groups (A: 7.2 mm versus B: 6.9 mm, ns) as was the BMI (A: 25.2 versus B: 25.1, ns). These results are summarised in table 3.2.

	Total	Group A	Group B
Number patients	582	538	44
Median age (range)	50 years (16-86)	50 (16-86)	48 (24-72)
Female	378 (65%)	349 (65%)	29 (66%)
Male	204 (35%)	188 (35%)	16 (34%)
Number of treated legs	644	599	45
Primary varicose veins	534/644 (83%)	491/599 (82%)	43/45 (96%)
Recurrent varicose veins	110/644 (17%)	108/599 (18%)	2/45 (4%)
C ₂ Varicose veins	361/644 (56%)	321/599 (54%)	40/45 (89%)
C ₃ Oedema	59/644 (9.2%)	56/599 (9%)	3/45 (7%)
C ₄ Skin changes	172/644 (26.7%)	170/599 (28%)	2/45 (4%)
C ₅ healed ulcer	33/644 (5.1%)	35/599 (6%)	0
C ₆ active ulcer	19/644 (2.9%)	19/599 (3%)	0

C of CEAP score : Clinical, Etiology, Anatomy, Pathology (EAP is similar in all patients)

Table 3.1: Patient demography and disease severity assessment

Variables	Group A (n=599)	Group B (n=45)	“P” value
Total laser energy (J)	1877 (IQR 997-2350)	1191 (IQR 1032-1406)	<0.05
Energy Density (J/cm)	48 (IQR 37-59)	37 (IQR 30-46)	<0.01
Diameter of the vein* (mm)	7.2 (IQR 5.6-9.2)	6.9 (IQR 5.5-7.7)	0.28
BMI (Kg/m ²)	25.2 (IQR 23.0-28.5)	25.1 (IQR 24.3-26.2)	0.36
Length of treated vein (cm)	33 (IQR 27-39)	29 (IQR 24-35)	0.06

Table 3.2: Comparison of variables in the groups (IQR- inter-quartile range)

* Maximum diameter measured while patient is standing

Group A: Limbs with complete occlusion of the treated GSV

Group B: Limbs with either a patent or partially occluded GSV

The ED administered to individual limbs ranged from 22-82 J/cm and this was used to sub-group the treated limbs (table 3.3). The frequency of successful ablation was greater with increasing ED and when this was ≥ 60 J/cm GSV ablation was achieved in all limbs (100%). Importantly, a higher ED did not appear to influence complication rates and the frequency of ‘phlebitis’ in veins that received ≥ 60 J/cm or <60 J/cm was 7.4% (7/95) and 10.7% (59/549) respectively. This difference was not statistically significant (p=0.316).

Energy density (J/cm)	Number of limbs treated	Complete occlusion	% success	Phlebitis	Transient cutaneous numbness	DVT
<30	82	71	86.6%	9 (10.9%)	1	0
30 – 39.9	168	149	88.7%	16 (9.5%)	2	0
40 – 49.9	176	164	93.2%	19 (10.8%)	2	0
50 – 59.9	123	120	97.6%	15 (12.2%)	1	1
60 – 69.9	79	79	100%	7 (8.8%)	1	0
≥70	16	16	100%	0 (0%)	0	0
Total	644	599	93%	66 (10.2%)	7 (1.1%)	1 (0.2%)

Table 3.3: Success and complication rates according to energy density at 3 months

3.1.4 Discussion

The findings of this study form the basis for developing a standardised protocol for successful EVLA. It is clear that an ED of energy density $\geq 60\text{J/cm}$ is central to achieving complete GSV occlusion. This equates to 5 pulses/cm vein when using 12W power, 1s pulses and 1s intervals for laser fibre withdrawal i.e. 2mm pull-back during each 1s interval. Continuous withdrawal of the fibre using 14W power has subsequently been adopted in our unit as this has the benefit of reducing treatment times. Delivery of 60J/cm with this technique requires pull-back of 1cm of the laser fibre in 4.3s. For practical purposes a policy of withdrawing 1cm of fibre over 5s (70J/cm) has been adopted. That this is both efficacious and safe is confirmed by this study, and in particular complication rates were not influenced by delivery of higher levels of laser energy within the range used.

Other authors have also assessed the efficacy of different levels of energy delivery. Timperman reported similar data to that presented here, with a significant difference in laser energy delivery between “successes” and “failures” (63.4J/cm versus 46.6J/cm, $p < 0.0001$). In that study there were no treatment failures with an ED of $>80\text{J/cm}$ (Timperman et al., 2004) although in a subsequent study the same author treated 100 GSV with 95J/cm achieving successful ablation in 95% of limbs (Timperman et al., 2005). In contrast Kim et al achieved 100% technical success in 34 patients using a 980nm diode laser at 11W power, delivering 35.16J/cm (Kim et al., 2006). It is likely that a small study such as this reflects reporting bias rather than a real finding.

It has been suggested that reporting energy delivery as J/cm is an oversimplification and does not take vein diameter into account. Thus Proebstle found that laser fluence (laser energy per cm^2 vein) was a risk factor for non-occlusion (Proebstle et al., 2004) and that treatment regimes should be based upon this type of calculation. Such an argument may be flawed since vein diameter at the time of ablation is significantly reduced due to catheter-induced spasm following cannulation together with the effect of the tumescent anaesthesia. Further, the vein may not be of a uniform diameter and thus both calculation of fluence and the delivery of the appropriate laser energy to individual segments of vein are more difficult. A protocol based on J/cm seems more practical and despite the author’s apparent enthusiasm for calculating laser fluence Proebstle has also reported results that are similar to those presented here (Proebstle 2006) in a study assessing the difference between a 15- or 30-W power supply at 3- and 12-month follow-up ablation with a 940-nm laser. In this study the average energy densities were 23.6 J/cm (15-W) and 69.9 J/cm (30-W). They reported significantly more failures in the 15W group at 3 months and concluded that higher energy delivery leads to fewer failures. They proposed an energy density threshold of $\approx 60\text{ J/cm}$ of vein (Proebstle et al., 2006). Although another study has shown that energy density levels of up to 160J/cm can be used without an adverse outcome (Carradice et al., 2010). Prince et al. have shown that an energy density beyond 80J/cm is not associated with an increase occlusion rate. (Prince et al., 2008).

Interestingly, similar energy density levels (60-70J/cm) are delivered by the Closure FAST device (Proebstle et al., 2008; Almeida et al., 2009). That the energy required to achieve irreversible vein wall damage regardless of the mechanism of delivery seems logical.

Although the protocol described above is straightforward it may not be suitable for all interventions. If the vein for ablation is particularly superficial (within 1cm of skin surface) a reduction in energy density (50J/cm) might be considered to prevent skin burns although this is unnecessary if the vein is separated from the skin by ≥ 1 cm following administration of TA. The basis for this is a previous study by Beale et al which showed that the maximum perivenous temperature 10mm from the vein was 36⁰C (Beale et al., 2006) thus ensuring that skin burns will not occur. Nevertheless, in the popliteal fossa nerve injury could be critical but should be avoided by not exceeding 60J/cm. Conversely, in the proximal GSV, particularly in a large vein, the vein is usually deeper and up to 100J/cm can be safely used to ensure proximal occlusion.

This study has also shown that neither vein diameter nor the length of vein ablated had any influence upon success rates and these findings are not particularly surprising. The impact of BMI upon outcome was also examined since the efficacy of post-EVLA compression might have been reduced in obese patients. Although this did not seem to be an important factor conflicting data has been reported by Timperman who found a statistically significant difference in body mass index (BMI) between successes and failures [30 versus 46, p=0.0009] (Timperman et al., 2004). This difference could be explained by the absence of super-obese patients in our study.

Laser energy inflicts thermal injury to the venous endothelium and sub-endothelial collagen leading to fibrous sclerosis of the vein (Proebstle et al., 2002; Corcos et al., 2005; Bush et al., 2005) Although different wave length diode lasers (808-1470 nm) have been used for GSV ablation (Navarro et al., 2001; Min et al., 2001 ; Proebstle et al., 2002; Bush et al., 2005) this study

employed an 810 nm diode laser which proved to be safe, and effective (provided sufficient energy was used).

Successful EVLA depends upon inflicting sufficient vein wall damage to cause initial contraction and subsequent fibrosis of the treated vein rather than thrombosis which could lead to re-canalisation and treatment failure. In order to achieve this factors other than the quantum of thermal energy delivered to the vein are likely to be important. Adequate volumes of tumescent anaesthesia and treatment in the Trendelenburg position should ensure that the vein is empty and that the laser fibre is in close proximity to the vein wall. This should increase the certainty of achieving irreversible damage to the vein wall. Further, it ensures that the distribution of energy is more predictable and not dependent upon vein diameter or the volume of blood within the vein at the time of treatment.

In conclusion this study has shown that the ED (J/cm) of laser delivery is the main determinant of successful GSV ablation during EVLA and that delivery of ≥ 60 J/cm is required for optimum results. Neither GSV diameter nor BMI appeared to influence outcome. Finally, the frequency with which phlebitis occurred did not appear to be influenced by an energy density within the study range.

3.2 Study 2: Influence of Warfarin upon the efficacy of EVLA

3.2.1 Introduction

Endovenous laser ablation (EVLA) employs thermal energy to cause irreversible vein wall injury and thus occlusion of an incompetent truncal vein. The work described above has shown that laser energy density is the single most important factor that determines the efficacy of laser ablation and this is also confirmed by others (Mordon et al., 2006).

In the short term it is possible that thrombotic occlusion of the treated vein occurs in some veins (although it should be avoided provided the recommendations described above are followed) before vein contraction and fibrosis ensue. Thus it is possible that factors that inhibit thrombus formation such as anticoagulants may influence the success of EVLA.

Unlike surgery, EVLA may be particularly suitable for older patients and those with significant medical co-morbidities in whom the treatment of superficial venous reflux and varicose veins is indicated because of complications such as varicose eczema, lipodermatosclerosis and ulceration. A proportion of these patients may be prescribed long term anticoagulation with warfarin for their co-existent medical conditions. This would usually be stopped prior to conventional varicose vein surgery because of the risk of intra-operative bleeding. Further, in-patient as opposed to day-case surgery is usually required with the duration of admission prolonged if pre-operative conversion to heparin therapy is required or post-operative stabilisation of anticoagulant therapy necessary. A potential advantage of EVLA, given the absence of surgical incisions, is that anticoagulant therapy may not need to be stopped before treatment. It is unknown however whether continuing

warfarin therapy influences the success of truncal vein ablation. This study therefore examines this issue.

3.2.2 Methods

Patients

Of 393 patients who underwent EVLA for varicose veins between May 2005 and January 2007 at the General Infirmary at Leeds, 22 patients (median age 62 (51-77), 12 female, 10 male; 24 limbs) continued taking warfarin at the time of treatment (“warfarin group”) for isolated sapheno-femoral junction (SFJ) and GSV reflux. Outcomes in these patients were compared with those in 24 age/sex and disease-severity (CEAP) matched control patients who were not taking warfarin (“no-warfarin group”). The control patient for each study patient was the next patient who underwent EVLA in our department and fulfilled the inclusion criteria. Patients with concomitant reflux in both the SSV and GSV and those with deep vein reflux from a previous deep vein thrombosis (DVT) were excluded from the study. The indication for warfarin therapy in the study group was atrial fibrillation (n=14) or a metallic heart valve (n=8). Informed consent was obtained for the procedure and for data collection from all patients who received EVLA for varicose veins

Data collection

Prior to laser treatment all patients underwent DUS [TITAN®, Sonosite Inc, Bothell, USA, 5-10 MHz linear probe] to confirm the site of superficial venous incompetence. In addition the diameter of the GSV was measured 10cm distal to the SFJ, avoiding any localised dilatation. Suitability for GSV EVLA was established using criteria that have been described earlier in this thesis. Patients’ past medical history and drug history were documented. Disease severity was assessed using “C” of

the CEAP clinical classification⁴ (“EAP” of CEAP were the same for all patients). Disease specific quality of life was assessed using AVVS scores before and 1 year after treatment.

EVLA was performed using an 810nm diode laser (12W power, 1s pulses, 0.1s intervals) and tumescent local anaesthesia (0.1% lignocaine with adrenaline) as described earlier. Neither concomitant phlebectomies nor foam sclerotherapy were undertaken although the latter was performed at the first follow-up visit (6 weeks) for residual varicosities if requested by the patient. Treatment details including the laser energy density (J/cm) were documented.

During follow up patients were assessed at 6, 12 and 52 weeks for successful GSV ablation (DUS), the presence of residual or recurrent varicosities and changes in AVVS scores. The criteria for successful ablation have been described earlier. Patient satisfaction was assessed at 1 year using a 10cm VAS which was then calculated as a percentage. A log of complications was maintained throughout the study. This included the development of a deep vein thrombosis (DVT), phlebitis, nerve damage (sensory or motor), chronic pain, and pigmentation. All these were assessed clinically apart from DVT which was assessed both clinically and by DUS (at each visit). This is a prospective observational cohort study with two groups.

Statistical analysis

All data were tested for normal distribution and are presented as median (\pm inter-quartile range) unless stated otherwise. The AVVS before and after laser ablation were compared within a group using a Wilcoxon test and the improvements in AVVS between groups were compared with a Mann-Whitney U test. All analysis were performed using the statistical package SPSS® for Windows (SPSS (14), Chicago, Illinois, USA).

3.2.3 Results

Disease severity and the demographic data for the two groups are summarised in table 3.4. Pre and post treatment vein diameters were similar in both groups (table 3.5). Successful occlusion of the full length of the treated GSV was observed in 20/24 (83%) limbs in the “warfarin group” compared to 23/24 (96%) limbs in “no-warfarin group” ($p=0.347$). Although the overall laser ED was similar in the two groups, of the 4 patients in whom ablation was not achieved in the “warfarin group”, 3 patients received suboptimal laser energy densities (46, 44, and 52J/cm). In these patients the GSV was patent and compressible on DUS at 6 weeks suggesting primary treatment failure. This is endorsed by an unchanged maximal vein diameter in these patients (table 3.5). In the remaining patient who received 62J/cm laser energy the GSV was partially occluded at 6 weeks GSV but fully patent with reflux at 12 weeks. This is more likely to represent re-canalisation. Similarly, the patient in whom treatment failed in the “no-warfarin group” received 58J/cm laser energy and had a partially occluded vein at 6 weeks which had recanalised at 12 weeks. Interestingly, both of these patients showed a reduction in vein diameter during follow-up. These data are summarised in table 3.5. There were no treatment failures in either group between 3 and 12 months.

Characteristics	Warfarin (%)	No warfarin (%)
Male	10 (45%)	10 (45%)
Female	12 (55%)	12 (55%)
Age, median (range)	62 (51-77) years	62 (51-77) years
Number of limbs treated	24	24
CEAP: C2	13 (54%)	13 (54%)
C3	4 (17%)	4 (17%)
C4	4 (17%)	4 (17%)
C5	2 (8%)	2 (8%)
C6	1 (4%)	1 (4%)

Table 3.4: Demography and CEAP classification of patients undergoing EVLA

A significant improvement in AVVS occurred in both groups: “warfarin group”: 14.6 (8.9-19.1) to 3.8 (1.9-6.2), “no-warfarin group”: 13.9 (7.6-20.1) to 3.5 (2.2-6.4); $p < 0.001$. However, there was no difference in either the improvement between the groups ($p = 0.446$) or in patient satisfaction with their treatment and outcome (“warfarin”=92% versus “no warfarin”=90%, $p = 0.391$).

There were no instances of DVT in either group and only one patient in the “no-warfarin group” reported marked post-EVLA discomfort (“phlebitis”). None of the patients described either extensive bruising or haematoma formation in either group.

Patient/ Group	Laser energy (J/cm)	Total laser energy (J)	DUS findings (ablation status, reflux status and diameter)			
			Pre-EVLA	6 weeks	12 weeks	52 weeks
“warfarin” (1)	46*	1380	Patent, Reflux 7.6 mm	Patent, reflux 7.4 mm	Patent, reflux 7.6mm	Patient had successful re-do EVLA
“warfarin” (2)	44*	1408	Patent, Reflux 8.2 mm	Patent, reflux 8.3mm	Patent, reflux 8.1mm	Patient had successful re-do EVLA
“warfarin” (3)	52*	1456	Patent, Reflux 7.7 mm	Patent, reflux 7.9 mm	Patent, reflux 7.6 mm	Patent, reflux 7.5mm
“warfarin” (4)	62	2260	Patent, Reflux 8.4 mm	Partially occluded 7.8 mm	Patent, reflux 5.1 mm	Patent, reflux 4.9 mm
“no warfarin” (1)	58	2320	Patent, Reflux 7.3 mm	Partially occluded 7.0mm	Patent, reflux 4.3 mm	Patent, reflux 3.2 mm
Warfarin Group: Median (IQR)	64 (54-72)	1997 (1686-2350)	Patent, Reflux 7.9 ±2.1	Fully occluded 5.0±1.4	Fully occluded 3.1±1.3	Fully ablated not visible
No-warfarin Group: Median (IQR)	66 (55-74)	2016 (1640-2460)	Patent, Reflux 7.6 ±2.2	Fully occluded 5.2±1.5	Fully occluded 3.0±1.4	Fully ablated Not visible
P (warfarin vs no- warfarin)	0.09	0.15	0.19	0.21	0.24	-

Table 3.5: Treatment details, ablation status, vein diameter and presence of significant reflux (>1s) in patients with treatment failure at 6, 12 and 52 week follow-up compared to patients who had successful treatment in groups A and B

- 3 patients in “warfarin” group received suboptimal laser energy density(<60 J/cm)^{1,2,3}
- Warfarin patients 1, 2, 3 and 4 – subsequently had successful re-do EVLA at 6, 7, 13 and 18 months respectively
- No-warfarin patient 1 had US guided foam sclerotherapy at 12 months

3.2.4 Discussion

Unlike conventional surgery, EVLA ablates the incompetent truncal vein in-situ without the need for surgical incisions. When varicose vein surgery is performed on patients who are taking warfarin it is common practise to discontinue therapy 3 days prior to operation. Although conversion to peri-operative anti-coagulation is not usually required for patients with atrial fibrillation this would have been necessary for the 8 patients with a metallic heart valve who were included in this study.

It is important to note that the small sample size is a weakness of this study. Further, patients' warfarin therapeutic level was not assessed from blood on the day of the EVLA treatment but checked from the warfarin yellow book. This may potentially be another weakness of this study.

The results of this study show that EVLA is effective in most patients who continue to take warfarin throughout the treatment period. Although there were more treatment failures in these patients it seems likely that sub-optimal laser energy delivery at least contributed to this in most instances. Nevertheless it is probable that warfarin therapy also contributed to these failures and thus it is reasonable to conclude that a laser energy density of $\geq 60\text{J/cm}$ is required in these patients. Conversely, the temptation to use significantly higher energy densities in patients taking warfarin should probably be avoided since this is likely to be associated with a greater frequency of vein wall perforation and bruising. This did not seem to be the case in the present study delivering a median energy density of 64J/cm . Although the extent of bruising was not quantified patient satisfaction was no different to that in patients who were not on warfarin.

Even if warfarin therapy was the primary reason for these treatment failures successful ablation occurred in the majority of patients thus justifying both the adoption of this technique in these patients and the continuation of anticoagulant therapy. Further, all 4 failures subsequently underwent successful re-do EVLA.

A diode laser of 810 nm wavelength produces temperatures above 700 °C at the tip of the laser fibre (Weiss et al., 2002). Nevertheless the temperature recorded 3mm from the vein wall in the surrounding tumescent anaesthesia is only 43 °C (Beale et al., 2006). It is therefore clear that the vein wall absorbs a significant proportion of the thermal energy that is delivered. Although Probstle et al suggested that heat conduction from the laser fibre to the vein wall is the result of steam bubble formation in blood (Proebstle et al., 2002), a more recent study suggests that direct contact between the fibre and the vein is the most likely mechanism of action (Fan et al., 2008). These high temperatures result in a range of injuries to the vein including denaturation of protein, tissue desiccation, necrosis, and possibly carbonisation with charring depending on the temperature to which it is exposed. (Goldman, 1991; Fan et al., 2008). This type of transmural damage results in a progressive fibrosis and permanent occlusion of the vein rather than a temporary thrombotic occlusion (Proebstle et al., 2002; Fan et al., 2008) and previous studies have provided ultrasound-based evidence for this (Weiss et al., 2002). Data from the present study confirms that these same changes occur in patients who undergo EVLA whilst taking warfarin (figure 3.1). Thus anticoagulants do not appear to interfere with the process of fibrotic occlusion following EVLA.

It might be argued that foam sclerotherapy would be a satisfactory alternative to surgery and EVLA in patients taking warfarin. However a recent study suggests that this technique only results in patchy endothelial damage and minimal subendothelial injury (Ikponmwosa et al., 2008). Thus thrombotic occlusion is likely to be a major component of its (initial) success and anticoagulants could prevent this. Further studies are required to assess the impact of warfarin on the efficacy of foam sclerotherapy.

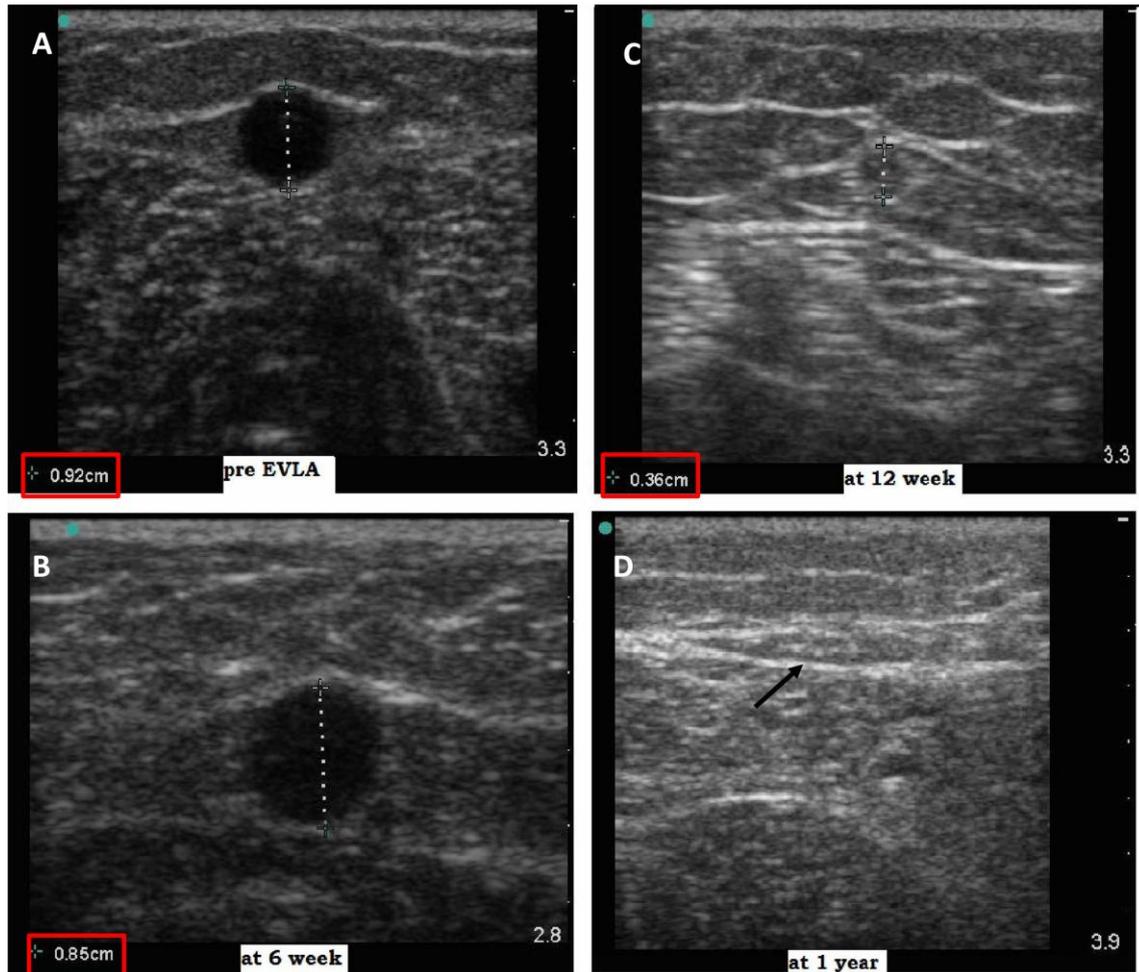


Figure 3.1: Sequential ultrasound appearance of GSV in a patient from the “warfarin group” after successful EVLA. These changes are identical to those occurring in patients who are not anticoagulated (Figure 4.1)

A): GSV pre-EVLA (9.2 mm, hypo-echoic, compressible)

B): GSV 6 weeks post-EVLA (8.5 mm, hypo-echoic, non-compressible, vein occluded). Note that this is a more magnified view than the pre-operative image.

C): GSV 12 weeks post-EVLA (3.6 mm, iso-echoic, not compressible, vein ablated)

D): GSV 1 year post-EVLA (non-visible - arrow shows empty saphenous space)

Given that EVLA appears an effective therapy for superficial venous incompetence in patients taking warfarin the risks of conventional surgery and the longer hospital stay associated with this in anticoagulated patients can be avoided. This will inevitably improve the cost effectiveness of treatment in these patients. Further, since patients who are taking warfarin are generally older and less fit than the majority of those requesting treatment for varicose veins the risks of intervention should be reduced. This may be particularly important given that these patients are more likely to require treatment for complications of their venous disease. That this is the case is reflected by a relatively high proportion of patients classified as C3-C6 in this study.

In conclusion, EVLA in patients who continue to take warfarin is safe and effective. Although warfarin can be continued during EVLA, adequate laser energy density or fluence should be administered to ensure a satisfactory outcome.

Chapter 4:

4. Structural changes and haemodynamic impact after EVLA

Using the standard technique for GSV EVLA the vein is ablated from 1cm distal to the SFJ to the level of knee leaving the below-knee GSV intact. This mirrors the current technique for GSV stripping during conventional surgery which is aimed at reducing the risk of saphenous nerve injury. However, unlike surgery, EVLA does not specifically treat the GSV tributaries at the SFJ and concomitant treatment of the superficial varicosities is not undertaken when following the original description of the technique. This chapter assesses the impact of EVLA on the following:

- 1) What happens to the ablated GSV?
- 2) What happens to the SFJ tributaries?
- 3) What happens to the distal (below-knee) GSV?

4.1 What happens to the ablated GSV?

4.1.1 Introduction

The majority [70%] (Labropoulos et al., 1994) of varicose veins are the result of SFJ and GSV incompetence. Although EVLA is initially effective (88-100%) in ablating the GSV, (Min et al., 2001; Min et al., 2003; Mundy et al., 2005) critics of the technique suggested that it induced thrombotic occlusion of the vein and was thus likely to be associated with a significant risk of re-canalisation rather than permanent occlusion. Further it was suggested that re-canalisation would result in a loss of any therapeutic benefit. This observational cohort study has investigated these two issues.

4.1.2 Methods

Patients

Seventy-three consecutive patients (84 limbs) underwent above-knee GSV EVLA for primary varicose veins due to SFJ/GSV reflux between March 2005 and November 2005 and completed 1 year follow up (Group A). A further group of 27 patients (Group B) with re-canalisation of a previously treated GSV were identified from a prospectively maintained database of patients undergoing EVLA during the previous 3 years. Group A assessed the current frequency of re-canalisation in our centre and acted as a control group for comparison with group B, all of whom had a re-canalised GSV.

Data collection

Pre-treatment disease severity was assessed using the CEAP classification, AVVS scores and VCSS. The maximum GSV diameter was measured whilst standing. All patients underwent EVLA using the stepwise withdrawal technique (810nm diode laser, 12W power) described earlier. The vein was ablated from the groin (SFJ) to the level of the knee. Following EVLA a duplex ultrasound scan (TITAN®, Sonosite Inc, Bothell, USA, 5-10 MHz linear probe) was performed at 6, 12 and 52 weeks to assess echogenicity, compressibility, diameter and flow status of the treated GSV. Absence of flow in a non-compressible vein or a non-visible GSV represented successful ablation. Re-canalisation was considered to have occurred when either antegrade or retrograde blood flow was observed in a compressible vein (segmental or full length). Compressibility and flow in the femoral and popliteal veins was assessed at each visit to exclude a deep vein thrombosis. The calf veins were not scanned unless the patient reported possible symptoms of a DVT. Foam sclerotherapy was used to treat any residual varicosities in the study limbs at 6 week follow up. AVVS and VCSS were reassessed at 1 year and clinical recurrence of varicose veins documented. All data were recorded prospectively in both groups of patients. For the purpose of disease severity comparison, patients with a re-canalised GSV in group A were analysed with group B in order to fully assess the impact of successful ablation.

Statistical analysis

Symptom improvement (AVVS, VCSS) was assessed using a Wilcoxon paired test within each group. Comparison between groups was performed using a Mann-Whitney U test and a student-t test employed to assess the metric data (vein diameter). All data are presented as median (\pm inter-quartile range) or as mean \pm standard deviation. All analyses were performed using SPSS® for Windows (SPSS, Chicago, Illinois, USA).

4.1.3 Results

Demographic data, the CEAP grading for the study limbs and the pre-treatment GSV diameters are shown in table 4.1. There was no difference in the maximum pre-treatment diameters in patients with an occluded or re-canalised vein. The treated length of vein was similar in both groups: 33 ± 8 cm in group A and 31 ± 6 cm in group B (table 4.2).

Characteristics	Group A (%)	Group B (%)
Male	31 (42%)	10 (37%)
Female	42 (58%)	17 (63%)
Age, median (range)	50 (26-76) years	51 (33-72) years
Number of limbs studied	84	27
CEAP-C2	46 (54.8%)	18 (66.6%)
C3	11 (13.1%)	4 (14.8%)
C4	19 (22.6%)	3 (11.1%)
C5	6 (7.1%)	2 (7.4%)
C6	2 (2.4%)	0

Table 4.1: Patients demographic details and the CEAP classification before EVLA

	Group A	Group B	p
Diameter of the vein (mm)	7.7 ± 2.0	7.9 ± 1.6	0.23
Length of vein treated (cm)	33 ± 8	31 ± 6	0.34

Table 4.2: Comparison of pre-treatment diameter of the vein and the length of vein treated between groups

Group A

The length of vein ablated was 33 ± 8 cm and the GSV was occluded in all 84 limbs (no flow, non-compressible vein) at 6 weeks. Subsequently 3/84 (3.5%) veins showed evidence of re-canalisation without significant reflux at 12 weeks. These veins remained patent with only flash reflux (<1s) at one year with no evidence of recurrent varicosities. There were no new instances of re-canalisation after 3 months. None of the post-EVLA scans showed any signs of deep vein thrombosis. In all patients the GSV diameter became progressively smaller during follow-up (table 3), with 70/82 (85%) being non-visible at 12 months. In 9 limbs a small (≈ 2 mm diameter) iso-echoic or hyper-echoic nidus remained visible within the saphenous space without a demonstrable lumen or flow. These veins were considered to be occluded. The ultrasound findings are summarised in table 4.3. Limbs in group A received a median of 66 (55-74) J/cm laser energy.

DUS findings	Pre-treatment (N=84)	6 weeks (n=84)	12 weeks (n=84)	1 year (n=82)
Diameter	7.7 \pm 2.0	5.1 \pm 1.3 *P<0.01	3.2 \pm 1.2 **P<0.01	2.6 \pm 0.7 (for the visible veins, n=12)
Hypo-echoic GSV	84 (100%)	62 (73.8%)	12 (14.2%)	0
Iso-echoic GSV	0	19 (22.6%)	60 (71.4%)	5 (6%)
Hyper-echoic GSV	0	3 (3.6%)	9 (10.7%)	4 (4.7%)
GSV non-visible	0	0	0	70 (85.4%)
GSV re-canalisation	N/A	0	3 (3.6%)	3 (3.7%)

Table 4.3: Comparison of the ultrasound findings of the treated segment of GSV before and after EVLA in group A

* pre-EVLA versus 6 weeks

** 6 weeks versus 12 weeks

Group B

Of the 27 patients in group B (31 ± 6 cm vein ablated), 3 had significant GSV reflux (>1 s) and persisting varicosities on their 6 weeks post-EVLA scan suggesting primary treatment failure. All were successfully re-treated with EVLA. Although 1 patient was taking warfarin and another had removed the compression bandage early, all had received low dose laser energy (44, 48, 38 J/cm) during treatment. The median laser energy for group B as a whole was 42 (37-55) J/cm. Primary failure of EVLA is suggested by the persisting large diameter (5.2, 6.4, 7.3 mm) of the GSV at 6 weeks compared to that of the other patients in group B who did not require re-treatment (3.0 ± 0.5 mm), including 6 patients with patent, small diameter veins and no or flash reflux at 6 weeks. The remaining 18 patients who received 44 (39-55) J/cm laser energy, had evidence of re-canalisation at 12 weeks following a satisfactory 6 week scan. During subsequent follow up these GSVs remained unchanged in size (2.9 ± 0.8 at 12 weeks v 3.0 ± 0.7 at 1-year; $p=0.33$) with no clinical evidence of recurrent varicosities. Finally, of 16/24 patients in group B who did not undergo repeat EVLA, DUS showed no reflux at 52 weeks (group B_{NR}) whilst 8 (group B_{TR}) had evidence of trickle reflux (reflux >1 s but only detectable on low-gain settings). The AVVS improved from 13.4 (8.2-19.4) to 2.5 (0.7-3.6), $p<0.001$ in group B_{NR} and from 14.8 (6.3-17.5) to 4.2 (2.2-8.1), $p<0.001$ in group B_{TR}. In both groups the GSV was significantly smaller at 1 year than before treatment (B_{NR}: 7.3 ± 2.5 mm v 3.1 ± 0.8 mm [$p=0.006$]; B_{TR}: 7.2 ± 2.3 mm v 3.0 ± 0.7 mm [$p=0.009$]).

Comparison of successful ablation and re-canalisation

At 1 year, the AVVS score improved from 15.1 (7.3-21.2) to 2.4 (1.1-4.2), $p<0.001$ and the VCSS from 4 (2-6) to 0 (0-2), $p<0.05$ in patients who had successful GSV ablation. Similar improvements were recorded in patients with GSV re-canalisation, excluding the 3 primary treatment failures: [AVVS: 14.2 (7.4-18.1) v 3.3 (2.1-5.5), $p<0.001$ and VCSS: 4 (2-5) v 0 (0-2), $p<0.05$]. There was no difference in the percentage improvement in the AVVS score between the groups (group A: 82.4% (60.1-98.2) v group B: 78.2% (55.3-92.3), $p=0.24$).

4.1.4 Discussion

Laser energy causes thermal injury to the endothelial and sub-endothelial layers of the treated vein leading to fibro-thrombosis (Proebstle et al., 2002 a; Proebstle et al., 2002b) of the vein. The relative lack of fibrosis during the initial post-treatment period results in the typical hypo-echoic appearance on ultrasound, similar to that of an acute thrombosis. With increasing fibrous tissue formation over time, the ablated GSV becomes iso-echoic or sometimes hyper-echoic before becoming non-visible by 1 year (Figure 4.1). Progressive development of fibrosis and contraction explains the gradual diminution in vein diameter following treatment. Further, re-canalisation of the GSV did not occur >3 months after EVLA, a finding confirmed by others (Min et al., 2003).

The results of this study suggest that when GSV re-canalisation occurs 6-12 weeks after treatment it is accompanied by vein shrinkage and continuing symptom relief, at least in the short term. Thus the symptomatic improvement was maintained at 1 year. Nevertheless longer follow-up is required to determine whether recurrent varicosities or symptoms subsequently develop.

Interestingly conversion of a large diameter GSV to a small, competent vein was the original aim of the radiofrequency RESTORE™ system (VNUS Medical Technologies, Inc, Sunnyvale, California) which was subsequently replaced by the CLOSURE device which aims to ablate the GSV permanently. Unlike the present data for group B, both symptoms and varicosities recurred in most patients following treatment with RESTORE (Manfrini et al., 2000).

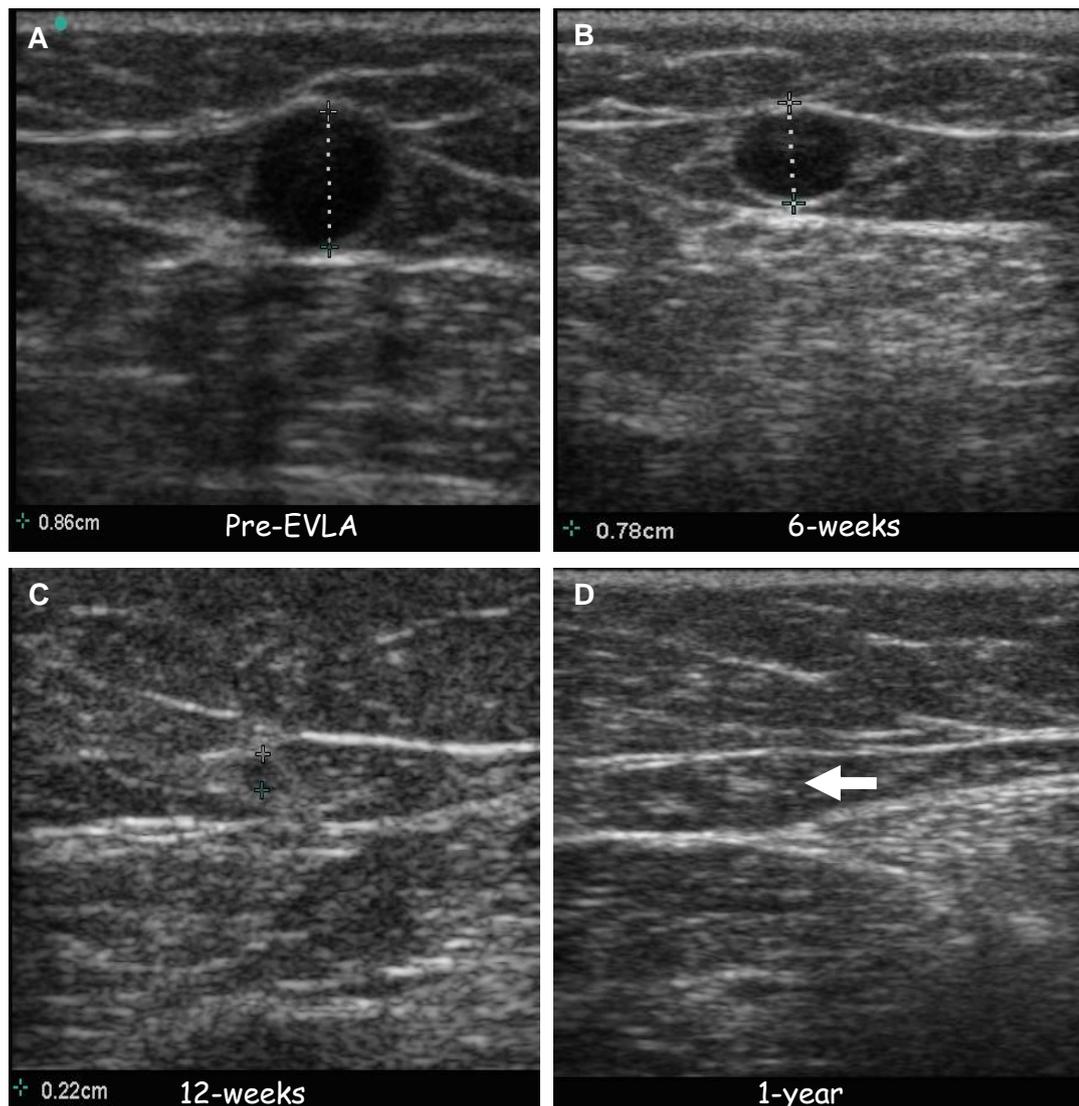


Figure 4.1: Ultrasound appearance of GSV after successful EVLA showing changes over time

A: GSV before EVLA (8.6 mm, hypo-echoic, compressible)

B: GSV 6 weeks after EVLA (7.8 mm, hypo-echoic, non-compressible: vein occluded)

C: GSV 12 weeks after EVLA (2.2 mm, iso-echoic, not compressible: vein ablated)

D: GSV invisible 1 year after EVLA (arrow shows empty saphenous space)

In 3/27 group B patients the GSV diameter remained unchanged from the pre-treatment value with significant reflux at the first follow up visit (6 weeks). It seems likely that these patients represent primary treatment failures. Such a conclusion is based on the low laser energy used in these patients, 2 of whom also had other possible reasons for non occlusion (warfarin, early removal of compression bandage). It is also possible that these veins had been temporarily occluded but underwent early thrombus dissolution allowing preservation of the pre-treatment vein diameter. Regardless of the cause of these early failures further treatment (repeat EVLA or surgery) is likely to be required for this small subgroup. Whilst other authors (Labropoulos et al., 2006) have suggested the use of ultrasound guided foam sclerotherapy following GSV re-canalisation this technique was not used in patients with a primary treatment failure because of the relatively high risk of further re-canalisation with this technique (Belcaro et al., 2003). Nevertheless it may have a role in patients with segmental re-canalisation. Although one of these patients was taking warfarin experience in other patients does not suggest that this, or antiplatelet drugs need to be discontinued prior to EVLA provided that $>60\text{J/cm}$ energy is delivered to the vein (Chapter 3).

The mechanism for re-canalisation between 6-12 weeks (the majority of “failures”) is also open to debate. Whilst thrombus dissolution is considered the most important factor intra-luminal neovascularisation may also play a role (Labropoulos et al., 2006). If this occurs it is believed that a patent vaso vasorum of the target vein continues to supply blood to the fibrothrombus in the vein lumen bringing growth factors that promote new vessel formation. Such neovascularisation may communicate with the patent vaso vasorum forming an intra-luminal arterio-venous fistula. Regardless of the mechanism re-canalised veins show evidence of a significant diameter reduction (Figure 4.2), with no or trickle reflux and resolution of symptoms. These patients do not require further treatment, at least within the first year. Further follow up of these patients is required to determine the medium / long term prognosis.

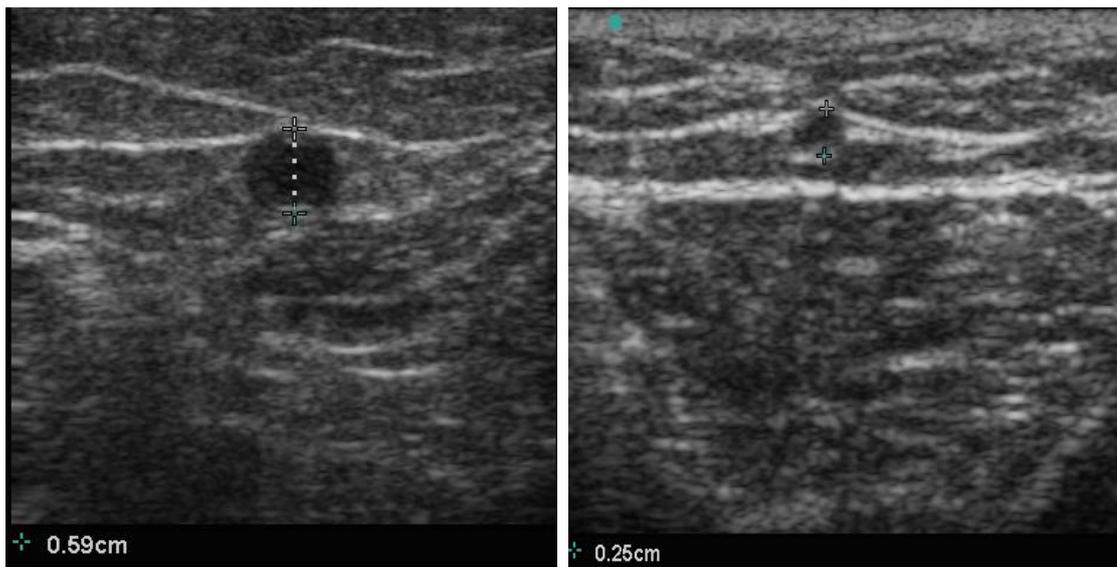


Figure 4.2: Ultrasound appearance of a re-canalised GSV at 3-months. Note the re-canalised GSV is small (2.5mm) compared to its pre-EVLA size (5.9mm)

In conclusion, the GSV diameter diminishes over a period of months following EVLA and most successfully ablated veins (85%) are not visible by 1 year. Using current treatment parameters ($\geq 60\text{J/cm}$ laser energy) GSV re-canalisation is uncommon (4%) and occurs within 3 months of treatment. In most cases re-canalisation does not lead to clinical recurrence or return of symptoms and does not require further intervention. In patients with early re-canalisation (primary treatment failure) repeat EVLA has proved successful.

4.2 Fate of GSV tributaries at the saphenofemoral junction

4.2.1 Introduction

The role of EVLA in the management of varicose veins secondary to SFJ and GSV reflux has already been discussed. One potentially important difference between this (and other minimally invasive therapies for varicose veins) and conventional surgical treatment is that the latter generally includes ligation of all SFJ/GSV tributaries in the groin in addition to GSV stripping and multiple avulsions. Since non-ligation of these tributaries is suggested as one of the causes of recurrent varicosities after surgery (Rivlin, 1975; Campbell, 1990; Redwood et al., 1994; Sarin et al., 1994) critics of EVLA have suggested that the durability of the technique might be compromised by failing to interrupt these veins. The fate of the untreated SFJ/GSV tributaries and their clinical significance following EVLA has therefore been investigated in this study.

4.2.2 Patients and Methods

Preliminary-study

Prior to undertaking this study, our ability to identify first generation SFJ/GSV tributaries using a portable high resolution duplex ultrasound scanner (TITAN®, Sonosite Inc, Bothell, USA) was assessed.

Twenty-four SFJs in 20 patients aged 33-61 years (12 females and 8 males) undergoing primary sapheno-femoral ligation were scanned (DUS). The number and configuration of first generation GSV tributaries within 5cm of the SFJ were drawn on a diagram. The diagrams were compared with the operative findings recorded on a similar diagram that was completed by a consultant vascular surgeon performing surgery. Only tributaries requiring ligation, rather than diathermy, were included.

Analysis of the DUS accuracy

A scoring system was developed to grade the accuracy of the DUS findings. On the operative drawing, which was considered the gold standard, each tributary requiring ligation was given a score of 2. Thus the maximum score was the number of the GSV tributaries X 2. The DUS drawing was then scored giving one point for identification of a tributary and another for determining its correct configuration. The maximum DUS score therefore equalled the operative score only if all the tributaries and their correct configurations were identified. The sensitivity was calculated as the total DUS score X 100%/ total maximum (operative) score.

Main study

Patients

Seventy patients who underwent GSV EVLA to treat primary symptomatic varicose veins due to isolated SFJ/GSV reflux between January 2005 and October 2005 were reassessed at one year. Patients who had reflux in more than one truncal vein who underwent EVLA, and those who had treatment for recurrent varicose veins were excluded from the study. Demographic details and the clinical severity of the varicosities are shown in table 4.4.

Demographic data	Number (%)
Male	28 (40%)
Female	42 (60%)
Age, median (range)	49 (29-72) years
Number of Limbs studied	81
CEAP: C2 (Symptomatic)	42 (52%)
C3	12 (15%)
C4	19 (23%)
C5	6 (7.5%)
C6	2 (2.5%)

Table 4.4: Patient demographic details and their CEAP classification

Data collection

In addition to the usual clinical assessments, pre-EVLA symptom severity was assessed using AVVS scores and VCSS. Data were recorded prospectively. Following EVLA, patients underwent serial duplex ultrasound assessment (TITAN®, Sonosite Inc, Bothell, USA, 5-10 MHz linear probe) of the GSV, the SFJ and the deep veins at 6, 12 and 26 weeks.

At 1 year follow up the limbs were examined to identify any residual or recurrent varicose veins, and the AVVS and VCSS re-assessed. Further, a detailed DUS was conducted to assess the SFJ and any tributaries. The GSV was examined from the knee (site of cannulation) to the SFJ and if visible checked for compressibility and flow status. Non visibility of the GSV or non-compressibility with absent flow in a visible GSV represented successful ablation. Careful DUS assessment of the SFJ was conducted by holding the probe longitudinally, horizontally and at different angles to identify any patent tributaries. The reflux status in these tributaries and the SFJ were assessed using colour flow. Patient satisfaction with the results of treatment was recorded using a visual analogue scale.

Statistical analysis

The changes in AVVS and VCSS after laser ablation were compared using a Wilcoxon test. Patients' satisfaction scores were compared using a two tailed unpaired student t-test. A "p" value of <0.05 was considered statistically significant.

Data are presented as median (\pm inter-quartile range) unless otherwise stated. All analyses were performed using the statistical package SPSS® for Windows, version 12 (SPSS, Chicago, Illinois, USA).

4.2.3 Results

Results of the preliminary study

In all patients DUS (TITAN®, Sonosite Inc, Bothell, USA) identified at least 2 first generation tributaries (Table 4.5). The overall score for DUS was 108 points compared to a maximum score of 122 points. The presence of 2 first generation tributaries was correctly identified in all limbs. When more tributaries were present it was more difficult to identify them all. However, the overall accuracy in identifying first generation tributaries of the GSV/SFJ was 88.5%.

No. 1st generation tributaries	Operative findings (No. limbs)	No. limbs with correct DUS findings	No. with inaccurate DUS findings (No. tributaries identified)
2	14	14	none
3	7	4	3 (2,2,2)
4	3	1	2 (2,2)

Table 4.5: The number of tributaries identified by DUS compared to operative findings

Results of the main study

At 1 year the treated segment of GSV was non visible on DUS in 77/81 (95%) limbs, iso-echoic (occluded) in 2/81 (2.5%) limbs and was patent in 2/81 (2.5%) limbs. There was no significant reflux in the 2 re-canalised GSVs, one of which was competent whilst the other demonstrated flash reflux (<1s). Thus 79/81 (98%) treated GSVs were successfully ablated resulting in a competent SFJ. None of the post-treatment duplex scans showed evidence of deep vein thrombosis. One or more patent tributaries were seen in continuity with the SFJ in 48/81 (59%) limbs - Group A. None of these tributaries demonstrated reflux. In 32/81 (40%) limbs (Group B) there was flush occlusion of the GSV with the SFJ and no tributaries were identified in

continuity with it. There was evidence of neovascularisation (with reflux) at the SFJ in one limb. In both patients who had a re-canalised GSV patent non-refluxing tributaries were identified.

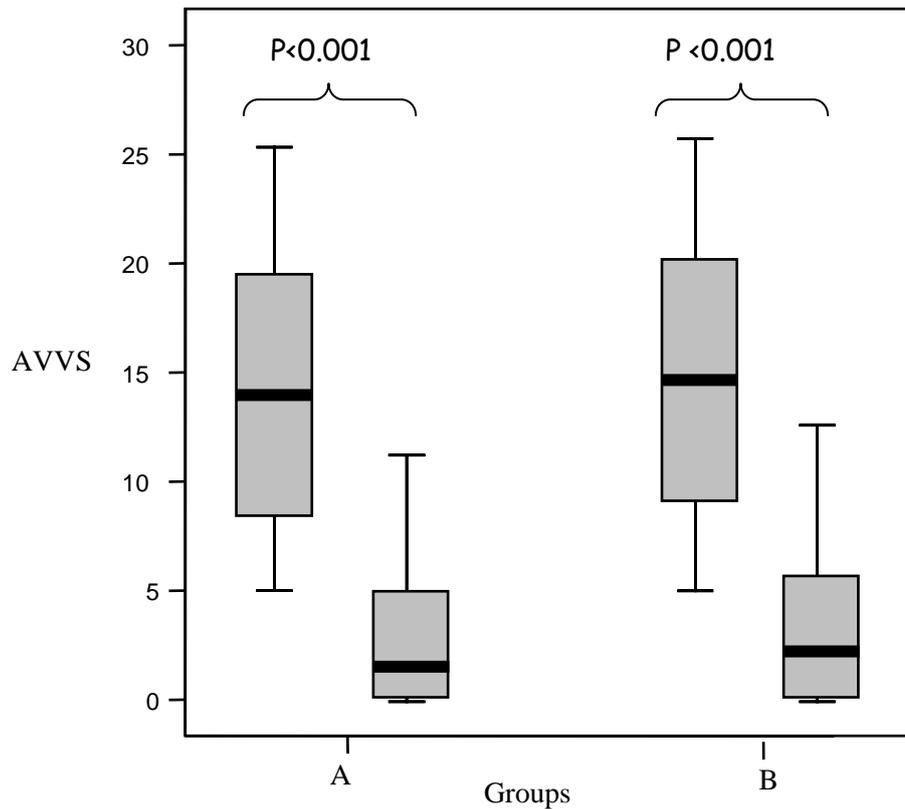


Figure 4.3: Box-plot graph comparing the pre-treatment & 1 year post-EVLA AVVS in patients with patent GSV/SFJ tributaries (Group A) and patients with no visible tributaries (Group B)

The AVVS were similar in both groups (Figure 4.3): Group A: pre-EVLA 13.9 (7.6-19.2), 1 year-follow-up 2.9 (0.6-4.8), $p < 0.001$; Group B: pre-EVLA 14.9 (9.2-20.2), 1 year follow-up 3.1 (0.8-5.1), $p < 0.001$, and there was no significant difference in the improvement in AVVS between the groups [Group A 9.8 (5.8-13.2); Group B 9.6 (6.1-13.6), $p = 0.27$; Figure 4.4]. Similarly, VCSS confirmed that the treatment effect was the same regardless of the presence of

patent tributaries [Group A: pre-EVLA 4 (2-5), follow-up 0 (0-3), $p<0.01$; Group B: pre-EVLA 4 (2-6), follow-up 0 (0-3), $p<0.01$; Pre-post reduction in score: Group A 4 (1-5), Group B 4 (1-6), $p=0.36$].

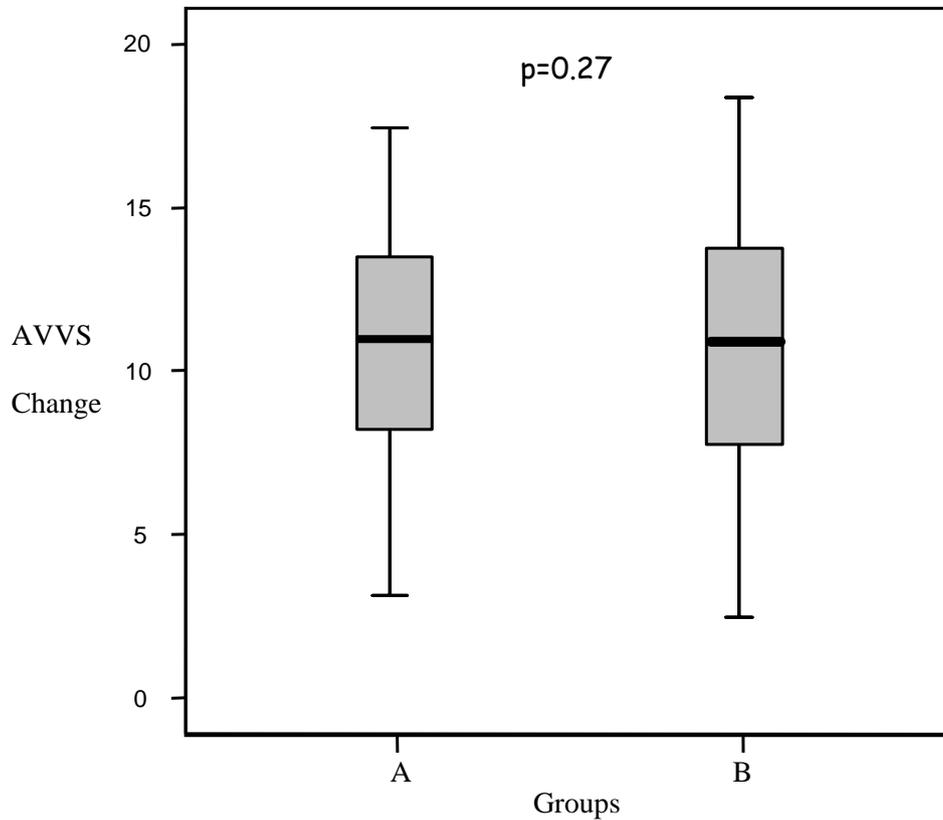


Figure 4.4: Improvements in AVVS in patients with patent GSV/SFJ tributaries (Group A) and in patients with no visible tributaries (Group B)

80/81 (99%) limbs had no residual or recurrent varicosities. In one limb, with no visible SFJ tributaries recurrence had developed due to an incompetent mid thigh perforator. Patient satisfaction was similar in both groups: Group A 92% and Group B 93% ($p=0.31$).

4.2.4 Discussion

Ultrasound is operator dependant and detecting GSV tributaries at the SFJ may be difficult. However, comparison with surgical findings has shown that high resolution DUS can be used to identify these with an acceptably high sensitivity. Although defining the precise anatomy of a complex junction may be a challenge, two or more tributaries were identified in all patients.

EVLA was very effective in ablating the GSV resulting in a competent SFJ in all patients. Further, in 40% of the treated limbs, there was flush ablation with the femoral vein leaving no tributaries in continuity with the SFJ. Although, one or more tributaries were seen in continuity with SFJ in the remainder, these tributaries were all competent. Symptom improvement or recurrence was not influenced by the presence of patent tributaries that were in continuity with SFJ.

Reflux from an incompetent SFJ may be distributed into the GSV and/or one of the other main tributaries such as the anterior accessory great saphenous vein (AAGSV). Reflux into more than one tributary is uncommon. Although there is little published data about this our experience of screening patients as to their suitability for EVLA suggests that it occurs in <5% patients. During the treatment of varicose veins all of the tributaries of the SFJ or proximal GSV that demonstrate reflux require ablation in order to achieve a successful outcome, and this concept is as important when endovenous treatments are performed as it is when surgery is undertaken. At operation, it is generally believed that the competent tributaries of the proximal GSV should also be ligated to reduce the risk of recurrence. However some authors argue that ligation of competent tributaries is unnecessary and it may promote neo-vascularisation (Chandler et al., 2000).

During EVLA, only the main trunk that has reflux, commonly the GSV is treated with no specific attempt being made to treat other tributaries. However, when the tip of the laser fibre is positioned 0.5-1.0cm from the SFJ (Min et al., 2001) the proximal extent of ablation may be

influenced by several factors. These include the anatomical configuration of the tributaries, the quantum of laser energy delivered and the efficacy of post-EVLA compression.

The initial concept of EVLA was that vein wall injury, leading to occlusion, was the result of heat transmission to the vessel by blood (Proebstle et al., 2002a). Distal to the groin this seems unlikely because of vein spasm around the catheter, venous compression (both manual and from tumescent anaesthesia) and because patients are treated in the Trendelenburg position. However, at the proximal end of the GSV it is more likely that some blood remains within the lumen and conducts thermal energy more proximally. This is a potential mechanism for flush occlusion of the GSV and occlusion of the tributaries (Figure 4.5). Support for such a mechanism is suggested by the ultrasound visualisation of steam bubbles in the proximal GSV during EVLA (Figure 4.6).

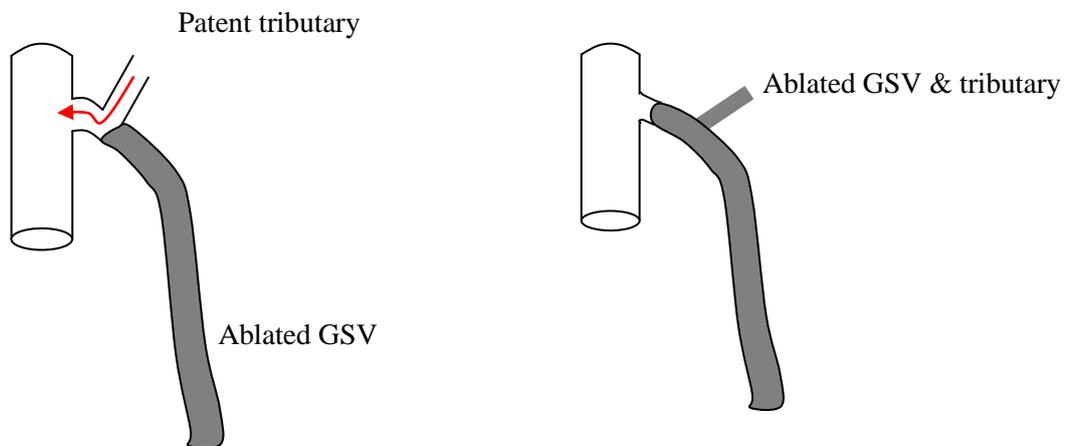


Figure 4.5: Non-flush and flush laser ablation of GSV

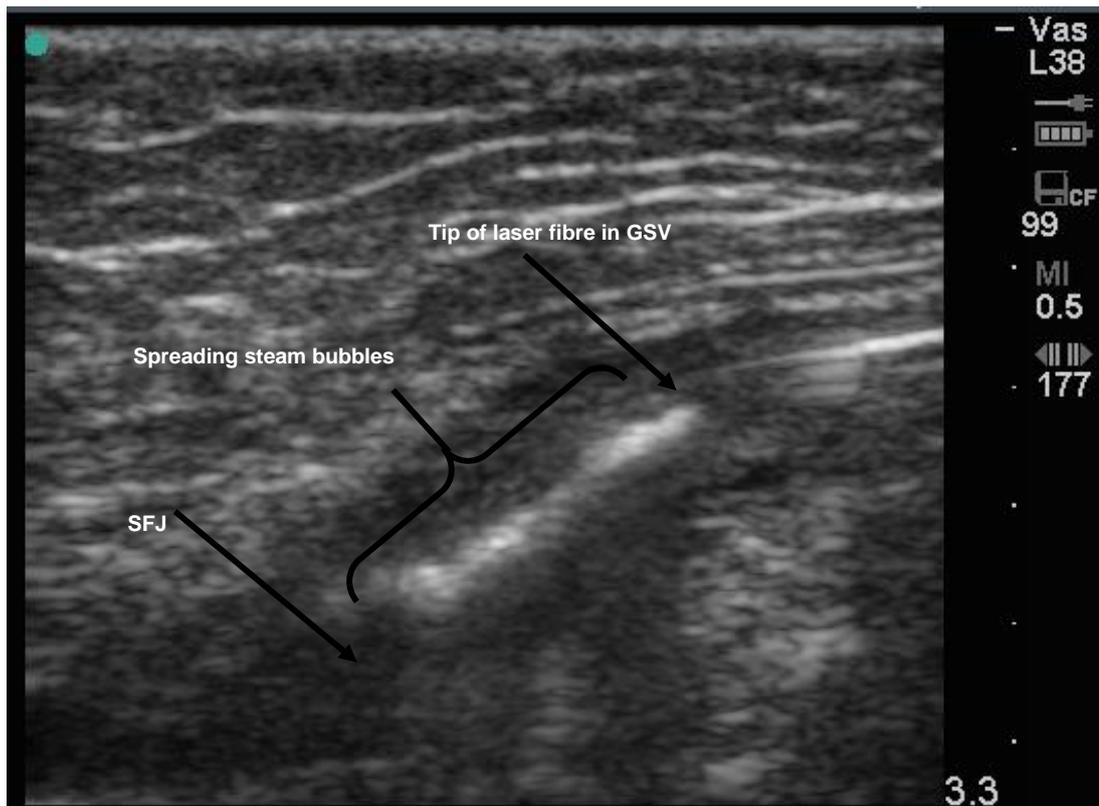
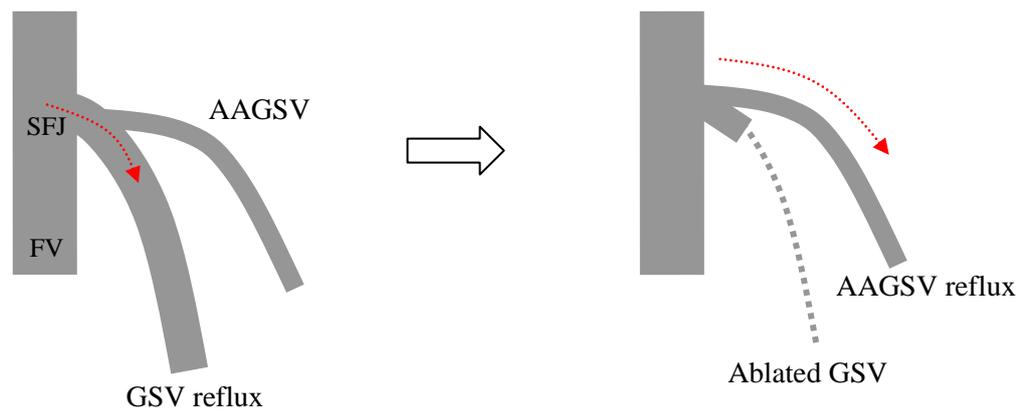


Figure 4.6: Ultrasonic appearance of steam bubbles in the proximal GSV during EVLA

That flush occlusion of the GSV does not occur in all patients presumably reflects variable transfer of heat into the proximal GSV. It may also be related to the efficacy of post-operative compression bandaging although it is unlikely that this is particularly effective in the groin, even in patients in whom flush ablation is achieved.

The results of this study indicate that the GSV/SFJ tributaries at the groin may or may not be ablated following EVLA. If they remain patent reflux into an untreated tributary (AAGSV, duplex saphenous system) is possible and could lead to recurrent varicose veins (Figure 4.7) but this seems rare.



Incompetent SFJ with GSV reflux

Incompetent SFJ with AAGSV reflux

Figure 4.7: Possible para-reflux following ablation of GSV that had reflux

In summary this study does not suggest that leaving non-refluxing tributaries in the sapheno-femoral junction is detrimental to the patient. At one-year follow up clinical examination for recurrence, the improvement in AVVS or VCSS scores and the degree of patient satisfaction were the same regardless of tributary patency. In one patient with recurrent varicosities this was the result of an incompetent thigh perforator. In addition only 1/81 limbs showed evidence of neo-vascularisation which is believed to be the commonest cause of recurrence following surgery (Jones et al., 1996; van Rij et al., 2004).

4.3 Fate of untreated below-knee GSV

4.3.1 Introduction

The original technique for EVLA as described by Min et al. comprised treatment of the above-knee GSV [AK-GSV] (Min et al., 2001), thus mimicking stripping of the AK-GSV during surgery. The subsequent reflux status of the below-knee GSV (BK-GSV) and its clinical significance following proximal GSV ablation have not been assessed previously and this issue has been addressed in this study.

4.3.2 Methods

Patients

All patients attending the venous clinic at The General Infirmary at Leeds between March 2005-December 2005 following standard endovenous laser ablation of the AK-GSV for varicose veins due to SFJ/GSV reflux were included in the study. Sixty nine limbs in 64 consecutive patients (24 males, 40 females; median age 51 [IQR 40-61]) with diverse disease severity (C2:40, C3:9, C4:10, C5:7 and C6:3) were studied.

Data collection and Follow-up

Before treatment patients were assessed clinically and the AVVS score measured. Standard EVLA of the AK-GSV was performed using an 810 nm diode laser under tumescent anaesthesia as an out-patient procedure as described in Chapter 2. Patients were reviewed at 6 weeks to assess the presence of residual varicosities which were treated with foam sclerotherapy if required. A duplex ultrasound scan (DUS) was performed at 6 and 12 weeks to confirm ablation or otherwise of the AK-GSV. Absence of flow in a non-compressible vein represented successful ablation. In addition the patency and reflux status of the BK-GSV (knee-ankle) were determined. Limbs were allocated to one of 3 groups depending on the findings: group A: no

reflux; group B: flash reflux <1s duration; group C: significant reflux >1s. The AVVS was re-measured at 6 weeks.

Statistical analysis

The AVVS scores before and after laser ablation were compared within a group using a Wilcoxon test. The improvement in AVVS between groups was compared by a Mann-Whitney U test. Sclerotherapy requirements were compared between groups using a Fisher's exact test. A p value of <0.05 was considered significant. Data are presented as median (\pm inter-quartile range) unless stated otherwise. All analysis were performed by the statistical package SPSS® for Windows (SPSS (14), Chicago, Illinois, USA).

4.3.3 Results

Complete occlusion of the treated length of AK-GSV and SFJ competence were confirmed in all (69/69) limbs. Conversely, the distal untreated BK-GSV was compressible and patent in all limbs (69/69). Of these 34/69 (49%) had normal forward flow without reflux (Group A), 7/69 (10%) had flash reflux (Group B), and 28/69 (41%) had significant (>1s) reflux (Group C) in the untreated BK-GSV (Figure 4.8). No incompetent calf perforators were identified in these patients. All three groups showed a significant improvement in AVVS at 6 weeks, Group A: 14.6 (8.4-19.3) v 2.8 (0.5-4.4), Group B: 13.9 (7.5-20.1) v 3.7 (2.1-6.8), group C: 15.1 (8.9-22.5) v 8.1 (5.3-12.6); $p < 0.001$ for all three groups. Percentage improvement in AVVS was 86.2%, 82.1% and 59.1% in groups A, B and C respectively (Figure 4.9). The improvement in AVVS was significantly ($p < 0.001$) lower in group C compared to the other two groups.

Delayed foam sclerotherapy was required in 44% (30/69) of treated limbs. In group C this was necessary in 25/28 (89%) patients compared to 4/34 (12%) in group A and 1/7 (14%) in group B. The sclerotherapy requirement for group C was significantly higher than that for groups A and B ($p < 0.001$).

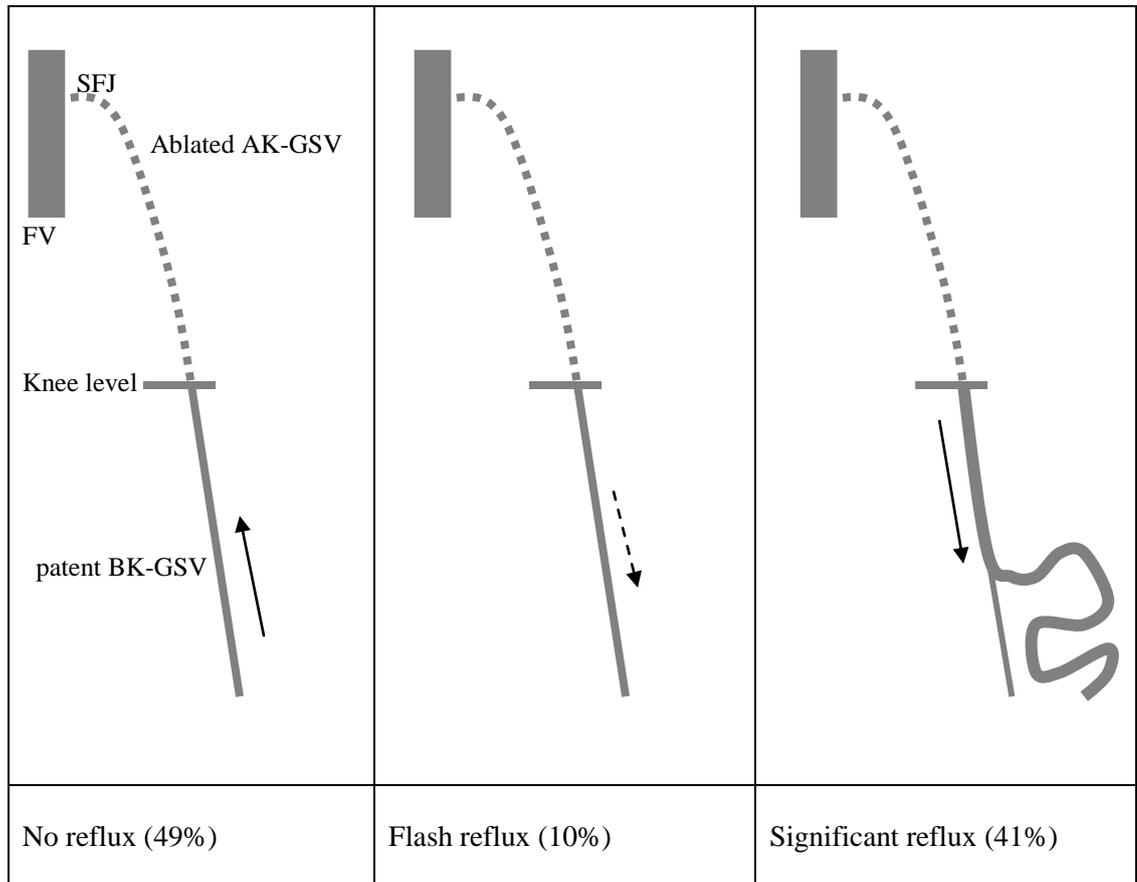


Figure 4.8: Reflux status of the patent below-knee GSV after above knee laser ablation

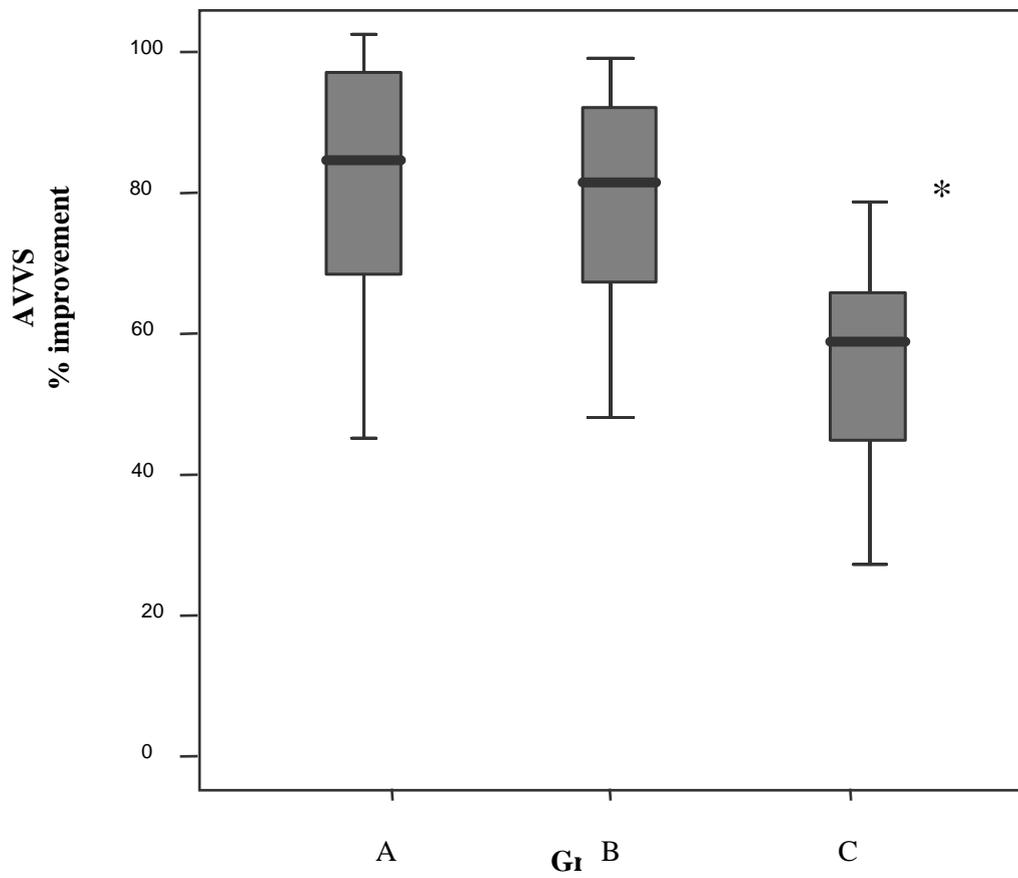


Figure 4.9: Percentage improvement in AVVS scores for groups A, B and C

(* $p < 0.001$ versus groups A and B)

4.3.4 Discussion

The original concept of EVLA, as described by Min et al was that laser ablation of the AK-GSV would eliminate sapheno-femoral and GSV reflux in the same way as sapheno-femoral ligation and GSV stripping during conventional varicose vein surgery. Following EVLA the BK-GSV remains patent in most patients. Rarely, it may become occluded secondary to thrombophlebitis. Thus, in the majority of patients blood from the BK-GSV will drain into the deep veins via calf perforators or other competent tributaries. Persisting reflux in the BK-GSV will occur in the presence of incompetent perforating veins in the proximal calf, although this was not evident in any of the patients included in this study. Duplex scanning however showed that in patients with persisting BK-GSV reflux a patent tributary was in continuity with the untreated GSV and that ante-grade flow in this tributary appeared to promote continuing GSV reflux (Figure 4.10).

Varicosities arising from the GSV may have several communications. Following ablation of the AK-GSV all the varicosities that are directly connected to this segment of vein tend to diminish in size, and may disappear. In contrast, varicosities that are in direct continuity with an incompetent BK-GSV will continue to receive blood from this and will persist following successful ablation of the proximal AK-GSV. Although, surgical phlebectomy or foam sclerotherapy will obliterate these residual varicosities it is logical to assume that the requirement for additional treatment may be reduced if the incompetent GSV from the SFJ to the lowermost point of reflux is ablated.

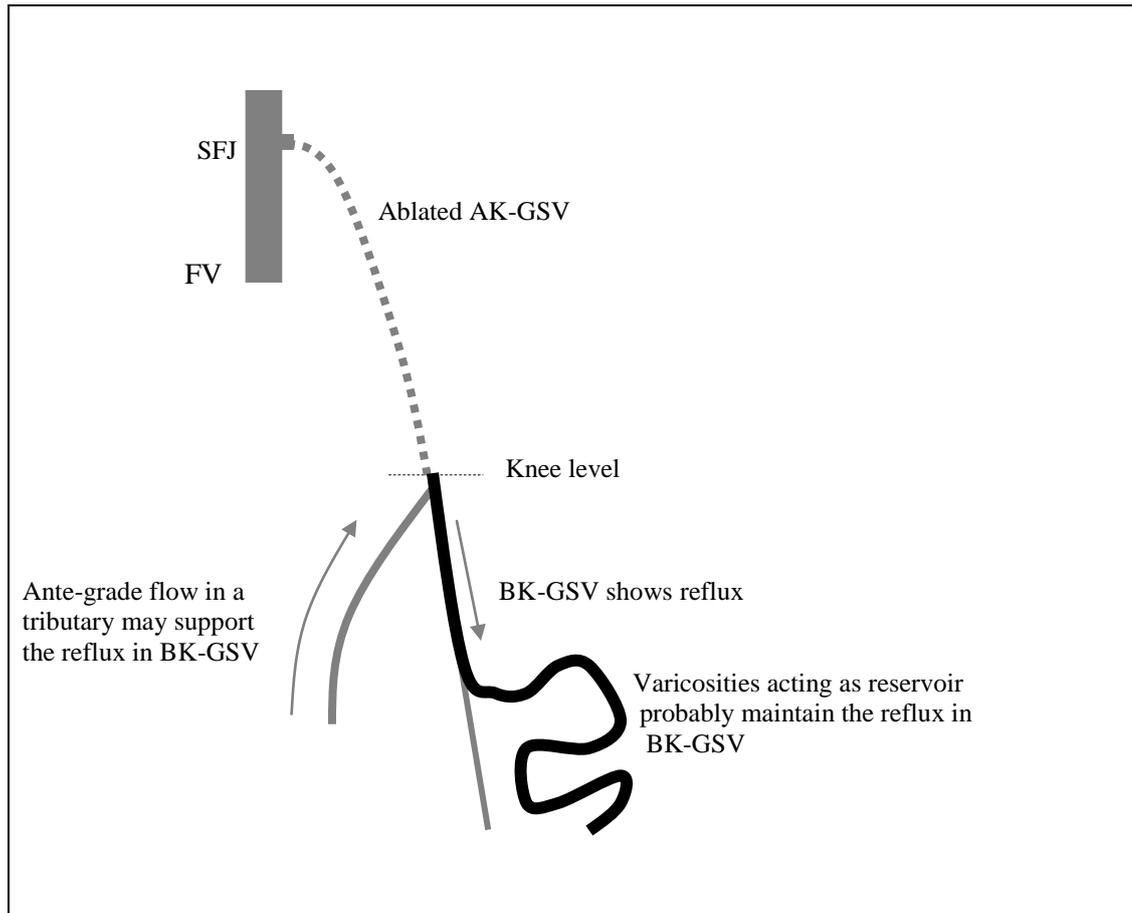


Figure 4.10: The potential mechanism for persisting BK-GSV reflux following successful EVLA of the AK-GSV

Some 44% of limbs in this study required delayed sclerotherapy for residual varicosities after laser ablation of the AK-GSV. The majority of these patients had persistent reflux in the BK-GSV in whom 89% underwent delayed foam sclerotherapy. The optimum treatment for residual varicosities after EVLA has been debated with both delayed sclerotherapy and concomitant phlebectomies (Mekako et al., 2007) having their proponents. The latter policy, even on the basis of the results presented here would mean that 56% of the whole group would undergo unnecessary phlebectomy, as well as requiring the use of an operating theatre for their treatment, thus increasing treatment cost. Abolition of reflux throughout the incompetent GSV should significantly reduce the need for adjuvant therapy for the superficial varicosities.

The results of this study confirm that ablation of AK-GSV results in symptom improvement regardless of the reflux status of the BK-GSV, although the benefit was significantly reduced in the presence of persistent BK-GSV reflux. This finding is not entirely surprising since previous studies have shown that the anatomic extent of reflux correlates with the symptoms and signs of venous disease (Labropoulos et al., 1996). Further, a recent study has shown that persisting BK-GSV is responsible for symptoms following surgical stripping of the AK-GSV (van Neer et al., 2006). This lends further support to the concept that ablation of a longer length of an incompetent truncal vein might result in a better clinical outcome.

Although these results suggest that persistent reflux in the BK-GSV is responsible for residual symptoms and more residual varicosities, it is not possible to comment upon the pre-treatment reflux status of the below-knee GSV since this was not recorded. Nevertheless, it is tempting to suggest that ablation of the BK-GSV, when reflux is present prior to EVLA, will provide improved symptom relief and reduce the requirement of subsequent sclerotherapy.

Minimally invasive options for ablation of an incompetent BK-GSV include EVLA and ultrasound guided foam sclerotherapy. Although laser ablation might be associated with the risk of thermal injury to the saphenous nerve below the knee this seems unlikely on the basis of previous temperature studies (Beale et al., 2006) and the safe use of laser therapy for small saphenous vein ablation in the popliteal fossa (Proebstle et al., 2003).

In conclusion, the presence of persisting reflux in the below-knee GSV appears responsible for both persisting symptoms of venous disease and residual varicosities following AK- GSV EVLA. Ablation of the below-knee GSV at the initial treatment may prove more effective in both respects and further studies are required to assess this hypothesis.

Chapter 5:

5. Randomised controlled trial: Does standard above-knee great saphenous vein EVLA provide optimum results in patients with both above and below-knee reflux?

5.1 Introduction:

The data presented in Chapter 4 showed that 44% patients required treatment for residual varicosities after routine AK-GSV EVLA. Further, symptom relief was less and the requirement for delayed sclerotherapy was greatest when there was persistent reflux in the BK-GSV. It therefore seemed logical to perform a randomised controlled trial to compare the efficacy of two different techniques for correcting both above and below-knee GSV reflux against the standard above-knee EVLA technique. The hypothesis for the study was that ablation of a longer segment of incompetent GSV would reduce the requirement for treating residual varicosities and provide additional symptom improvement.

5.2 Methods

The study was approved by our institutional ethics committee (appendix C) and was registered as a Current Controlled Trial (ISRCTN 31316759). It was conducted between October 2005 and June 2007 at The General Infirmary at Leeds. Patients with below-knee varicosities associated with both above and below-knee GSV reflux were invited to participate provided that they wished to undergo EVLA and were suitable for this technique. Patients were excluded from the study if they had: recurrent varicose veins, concomitant reflux in another truncal vein or perforator, allergy to sodium tetradecyl sulphate (STD), BK-GSV tortuosity precluding EVLA, a competent BK-GSV, age <18 years, or did not give informed consent. Participants were

recruited from 114 consecutive patients with varicose veins due to isolated sapheno-femoral and GSV reflux. They were randomised (block randomisation) to one of three treatment groups (figure 5.1). A sealed envelope method was used for randomisation and this was opened just before the treatment.

Power Calculation

This study planned to compare the follow-up sclerotherapy requirement across groups, to see if one modified treatment technique is significantly better than the other technique. From our pilot study we found that following standard EVLA 48% require follow-up sclerotherapy and the mean number of required sclerotherapy sessions was 0.66 (standard deviation 0.812). For this study we are expecting the sclerotherapy requirement to be halved with the modified technique. Analysis will be performed using two sample t-tests of equal proportions. Calculations are for 80% power at a 5% level of significance with 32 subjects required per group."

Inclusion Criteria

- Primary varicosities due to SFJ/GSV reflux
- Below knee varicosities due to reflux in both the above and below-knee segments of the GSV

Exclusion criteria

- Recurrent varicose veins
- Concomitant reflux in another truncal vein
- Patients with known allergy to STD
- No reflux in below-knee GSV
- Age under 18 years
- Not willing to take part in the study

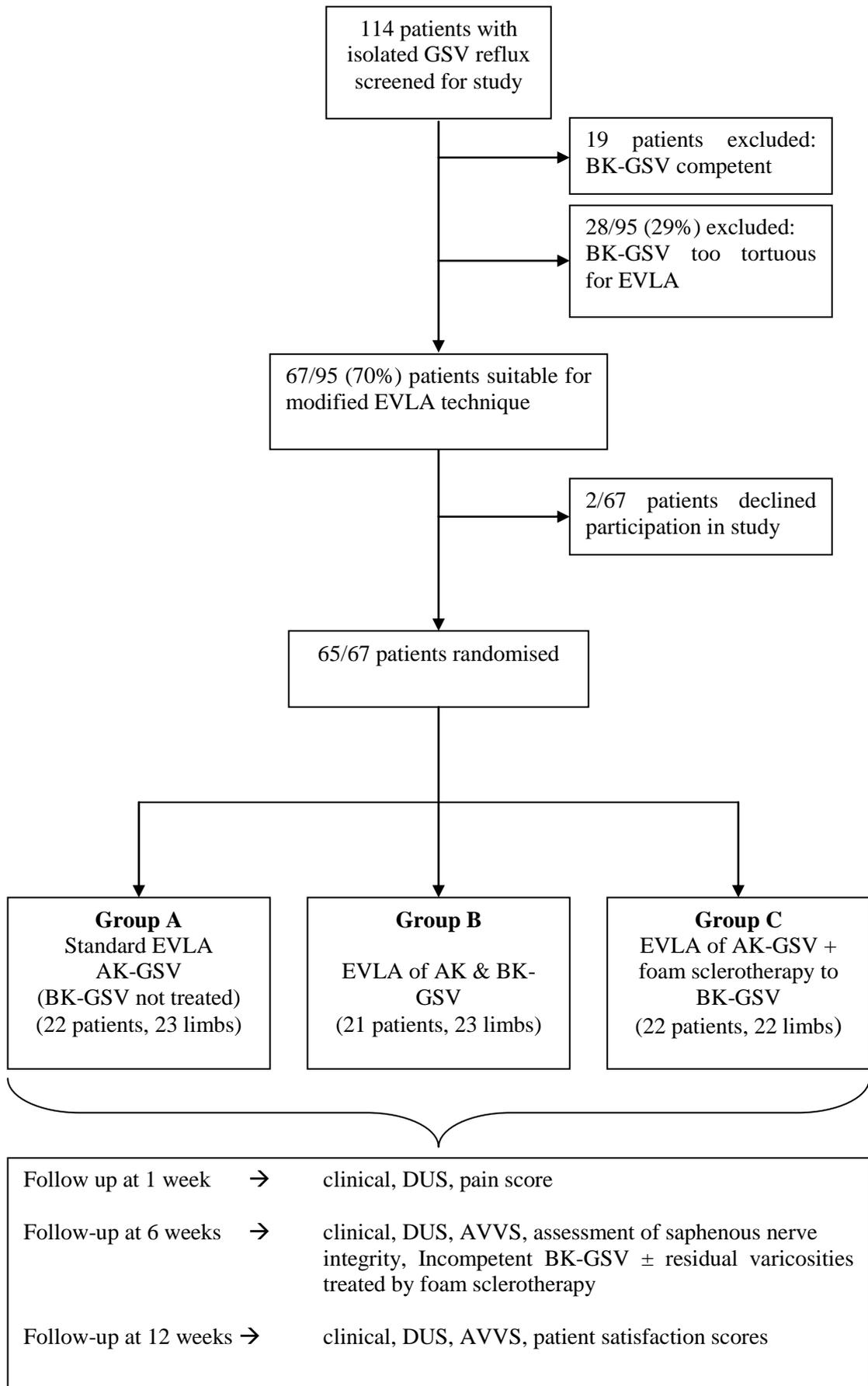


Figure 5.1: Details of randomisation and RCT protocol

5.2.1 Treatment

Group A underwent standard AK-GSV EVLA whilst in group B, EVLA was used to ablate the incompetent GSV from mid-calf to groin. Patients in group C underwent A-K EVLA with concomitant catheter-delivered foam sclerotherapy for their BK-GSV reflux. No patients were given synchronous sclerotherapy to their superficial varicosities at the time of EVLA. As EVLA was performed using local anaesthesia with immediate mobilisation DVT prophylaxis was not used.

Group A: standard above-knee EVLA

The GSV was cannulated at or just above (<5cm) the knee joint and a 5F (1.67mm) endovenous catheter (ELVeS™ Plus Katheter; Biolitec Group, Bonn, Germany) was passed over a guidewire. The catheter tip was positioned 1cm distal to the sapheno-femoral junction (SFJ) and EVLA performed as described in Chapter 2 using an 810 nm diode laser (12W power) delivering energy at a density of 60-70 J/cm. Post –treatment management was also as detailed above.

Group B: above and below-knee EVLA

The technique was identical to that for group A except that the GSV was cannulated in the calf, either below the lowest incompetent tributary or 70cm from the sapheno-femoral junction if GSV reflux persisted beyond this point (catheter length 70cm). Laser energy was again delivered at 60-70 J/cm.

Group C: AK-GSV EVLA and concomitant BK-GSV foam sclerotherapy

The GSV was cannulated as in group B and the catheter positioned 1cm distal to the SFJ. Tumescence anaesthesia was infiltrated only from the knee upwards and EVLA performed from groin to knee. The laser fibre was then removed and the catheter gradually pulled back towards the cannulation site in the calf whilst administering 2.5-3 ml of 1% STD foam (Fibrovein ®, STD Pharmaceutical Products Ltd, Hereford, UK) to the below-knee GSV. The foam was

prepared according to Tessari's method (Tessari et al., 2001). A compression bandage was applied to the leg following treatment.

Group C was included in the study to assess the combined effect of AK-EVLA and BK-GSV sclerotherapy as this technique would be appropriate in patients in whom BK-GSV tortuosity precludes laser ablation. This technique might also provide optimum treatment if group B patients report significant rates of saphenous nerve injury.

5.2.2 Data collection and follow-up

Pre-treatment clinical severity was assessed using CEAP grading (Porter & Moneta 1995) and AVVS scores (Garratt et al., 1993). The GSV diameters in mid-thigh and mid-calf were recorded whilst standing as were the length of vein treated, details of laser energy delivery and the time taken to complete the procedure (skin preparation to off-table time). Following treatment patients completed a daily (for 1 week) visual analogue scale (1-100) to assess pain, and were reviewed at 1, 6 and 12 weeks. At each visit the study limbs were assessed clinically and by duplex ultrasound (DUS) to ascertain the reflux status (significant reflux = >1s measured by spectral trace analysis) of the SFJ and both the AK and BK-GSV. Absence of flow in a non compressible vein represented successful ablation. GSV diameters were recorded at each visit (The follow-up proformas are given as appendix).

At 6 weeks patients were assessed for the presence of residual varicose veins (visible, palpable superficial varicosities ≥ 3 mm diameter) and varicosities associated with BK-GSV reflux were treated by foam sclerotherapy of this vein. For isolated varicosities without truncal vein reflux foam sclerotherapy was administered to the varicosities themselves. Sclerotherapy was not performed for BK-GSV reflux (ultrasound) in the absence of visible varicosities. The AVVS was repeated at the 6 week visit.

At 12 weeks, limbs were again assessed for the presence of residual varicosities and AVVs was recorded. In addition, ablation or patency of the treated truncal vein was confirmed by DUS and patient satisfaction with treatment determined using a visual analogue scale (1-100). A log of complications was maintained throughout the study and all data were collected and recorded prospectively. Patients were specifically questioned about neurological symptoms which were objectively assessed if present.

Study end points

The primary end-points were the presence of residual varicosities requiring sclerotherapy and an improvement in the AVVS scores, a disease specific quality of life measure. The secondary end-points were pain scores, patient satisfaction and complication rates.

5.2.3 Statistical analysis

The sclerotherapy requirement for each group was compared using a Fisher's exact test. AVVS improvement within a group was tested using the Wilcoxon test and compared between groups by a Mann-Whitney U test. Pain scores and patient satisfaction were compared using a student-t test (unpaired). A "p" value of <0.05 was considered significant. Data are presented as medians (\pm inter-quartile range) unless stated otherwise. All analyses were performed with the statistical package SPSS® for Windows (SPSS-14, Chicago, Illinois, USA).

5.3 Results

Demographic details are given in table 5.1 and treatment details in table 5.2. At both 1 and 6 weeks DUS showed no retrograde SFJ flow and no groin tributary reflux in any of the treated limbs. Similarly, the AK-GSV was ablated (non-compressible, no flow) in all limbs of all 3 groups.

In group A the BK-GSV remained patent in all instances and 15/23 (65%) showed persistent reflux (>1s) at 1 week. Examination at 6 weeks confirmed that reflux (>1s) was still present in 12/23 (52%) limbs. For these, ultrasound guided foam sclerotherapy was administered to the BK-GSV.

	Group A	Group B	Group C
Age (range) years	40 (30-69)	42 (27-70)	46 (31-68)
Male	9	8	10
Female	13	13	12
Number of limbs treated	23 (22 patients)	23 (21 patients)	22 (22 patients)
CEAP:			
C2	16	15	14
C3	3	3	3
C4	3	4	4
C5	1	0	1
C6	0	1	0

Table 5.1: Patient demography and disease severity scores (C of CEAP)

CEAP score : C of Clinical, Etiology, Anatomy, Pathology

	Group A	Group B	Group C
Length of vein treated by EVLA (cm)	31 (29-34)	52 (49-60)	30 (28-33)
Length of vein treated by FS at primary treatment	Nil	Nil	19 (17-22)
Laser energy density (J/cm)	64 (60-71)	61 (59-70)	62 (58-71)
Duration of the procedure (min)	39 (32-47)	45 (40-56)	44 (40-56)

Table 5.2: Treatment details (FS: catheter delivered foam sclerotherapy)

In group B the BK-GSV was ablated in all cases (23/23) compared to 19/22 (86%) in group C. The 3 patent BK-GSVs in group C had persistent reflux and these were re-treated (ultrasound guided foam sclerotherapy) at 6 weeks.

At 12 weeks, the SFJ remained competent and the AK-GSV ablated (non-compressible shrunken vein with no flow) in all limbs. Similarly, the BK-GSV remained occluded in all group B and C patients but 2 limbs in group A showed significant (>1s) below-knee reflux despite previous foam sclerotherapy. A further 11 BK segments showed flash (<1s) reflux. Sequential DUS showed that following laser ablation (AK-GSV in all groups, BK-GSV in group B) there was a progressive, significant, reduction in vein diameter. After BK-GSV sclerotherapy (groups A and C) this had not occurred by 12 weeks. The results are summarised in tables 5.3 and 5.4.

	Group A		Group B		Group C	
	AK-GSV	BK-GSV	AK-GSV	BK-GSV	AK-GSV	BK-GSV
Pre-EVLA	7.9 (5.9-9.2)	5.4(4.8-6.0)	7.8 (6.0-8.9)	5.9 (4.7-6.3)	7.7 (6.1-9.1)	5.5 (4.7-6.1)
At 1 week	7.4 (5.9-8.9) p = 0.46	5.5 (4.9-6.1) p = 0.36	7.6 (6.0-8.7) p = 0.38	5.7 (4.6-6.2) p = 0.47	7.5 (6.1-9.0) p = 0.37	5.4 (4.5-6.1) p = 0.32
At 6 week	5.2 (3.6-6.4) p = 0.04	5.4 (4.8-6.1) p = 0.32	5.2 (3.5-6.4) p = 0.03	4.0 (3.1-4.8) p = 0.03	5.3 (3.6-6.5) p = 0.02	5.4 (4.3-6.0) p = 0.49
At 12 week	3.2 (2.1-4.0) p = 0.03	5.3 (4.6-6.0) p = 0.34	3.1 (2.2-3.9) p = 0.02	2.8 (2.1-3.3) p = 0.01	3.2 (2.2-4.1) p = 0.04	5.0 (4.0-5.9) p = 0.09

Table 5.3: GSV diameter (mm \pm IQR) before and after EVLA: p values relate to comparison with previous measurement within the same group (1 week v pre-EVLA; 6-weeks v 1 week; 12 weeks v 6 weeks)

		Group A (n=23)		Group B (n=23)		Group C (n=22)	
		AK-GSV	BK-GSV	AK-GSV	BK-GSV	AK-GSV	BK-GSV
At 1 week	Ablated/occluded	23 (100%)	0	23 (100%)	23 (100%)	22 (100%)	19 (86%)
	Patent, no or flash reflux	0	8 (35%)	0	0	0	0
	Patent, reflux >1s	0	15 (65%)	0	0	0	3 (14%)
At 6 week	Ablated/occluded	23 (100%)	0	23 (100%)	23 (100%)	22 (100%)	19 (86%)
	Patent, no or flash reflux	0	11 (48%)	0	0	0	0
	Patent, reflux >1s	0	12 (52%)	0	0	0	3 (14%)
At 12 week	Ablated/occluded	23 (100%)	10 (43%)	23 (100%)	23 (100%)	22 (100%)	22 (100%)
	Patent, no or flash reflux	0	11 (48%)	0	0	0	0
	Patent, reflux >1s	0	2* (9%)	0	0	0	0

Table 5.4: Reflux status of vein segments after EVLA (data for 12 weeks represent the combined effect of EVLA and delayed foam sclerotherapy)

* 2 limbs in group A required further DUS guided foam sclerotherapy at 12 weeks

The overall sclerotherapy requirements (to the BK-GSV or directly into superficial varicosities) by 12 weeks were 61% (14/23) in group A, 17% (4/23) in group B, and 36% (8/22) in group C. These difference were highly significant ($\chi^2=9.39$ (2 df), $p=0.01$ for overall data). The difference between groups A and B was also significant ($p=0.006$) but not that between B and C ($p=0.19$) or A and C ($p=0.14$).

Compared to pre-EVLA there was a significant improvement ($p<0.001$) in the AVVS score in all groups at 6 weeks (before sclerotherapy). These results are shown in table 5.5. The % improvement in AVVS at 6 weeks was 55.4%, 84.2% and 72.8% for groups A, B and C respectively and this was greater in groups B and C compared to group A ($P_{A-B}=0.011$, $P_{A-C}=0.015$). Following foam sclerotherapy at 6 weeks all groups showed a further improvement in AVVS at 12 weeks which was greater in group A (Table 5.5).

	Pre-EVLA	6 weeks	12 weeks
Group A	14.8 (9.3-22.6)	6.4 (3.2-9.1) p (pre-6wk) < 0.001	3.2 (0.5-4.9) p (6-12 wk) = 0.023
Group B	15.8 (10.2-24.5)	2.5 (1.1-3.7) p (pre-6wk) < 0.001	1.9 (0.5-2.4) p (6-12 wk) = 0.073
Group C	15.1 (9.0-23.1)	4.1 (2.3-6.8) p (pre-6wk) < 0.001	2.4 (0.6-3.9) p (6-12 wk) = 0.064

Table 5.5: Aberdeen varicose vein scores (AVVS) before and after EVLA

The significant improvement in AVVS in group A could have been the result of either a reduction in the number of residual varicosities or occlusion of the incompetent BK GSV (or indeed both). In order to assess this, the AVVS was recalculated after excluding the question relating to the appearance of the varicosities. Following this adjustment the significant improvement in AVVS remained indicating that ablation of the BK GSV following foam sclerotherapy had made an important contribution to the reduction in symptom severity score (Table 5.6).

Group A	Pre-EVLA	6 weeks	12 weeks
Overall AVVS	14.8 (9.3-22.6)	6.4 (3.2-9.1) p (pre-6wk) < 0.001	3.2 (0.5-4.9) p (6-12 wk) = 0.023
AVVS except for Q1	10.6 (8.1-19.3)	5.2 (2.9-7.2) p (pre-6wk) < 0.001	2.2 (0.3-3.8) p (6-12 wk) = 0.012

Table 5.6: Recalculation of AVVS excluding first question in group A before and after EVLA

Median pain scores (out of 100) at 1 week were 32 (12-45), 34 (10-40) and 36 (12-50) in groups A, B, and C respectively, with no difference between the groups [p=0.12 (A-B), 0.16 (B-C), 0.11 (A-C)]. Although some tenderness was recorded along the treated GSV in most limbs at 1 week, only 2 patients in group C reported persistent pain due to BK-GSV thrombophlebitis for which diclofenac sodium was prescribed.

Skin staining over the BK-GSV was visible in 2/22 (9%) limbs at 6 weeks in group C. This had faded significantly at 12 weeks but was still visible. No skin staining occurred after BK-GSV EVLA. Of the 26 limbs requiring foam sclerotherapy at 6 weeks (15 BK-GSV; 11 isolated varicosities) 4 (15%) developed marked tenderness of the treated vein and 6 (23%) skin staining.

Patient satisfaction rates at 12 weeks were 90% (A), 94% (B) and 90% (C) with no difference between the groups. Complications other than “phlebitis” were uncommon with 1 patient in Group C reporting transient numbness in the distribution of saphenous nerve. There were no instances of DVT (common or superficial femoral veins, popliteal vein) on DUS performed at 1 week.

5.4 Discussion

Compared to standard above-knee EVLA concomitant ablation (laser or sclerotherapy) of an incompetent below-knee GSV resulted in fewer residual varicosities and superior symptom relief at 6 weeks. Further, these techniques reduced the subsequent requirement for delayed foam sclerotherapy. This study also confirms that both below-knee GSV EVLA and foam sclerotherapy are safe. Although randomisation of more patients might have resulted in significant differences in symptom improvement (AVVS) and sclerotherapy requirements between groups B and C this was considered unnecessary once it became apparent that EVLA of the BK-GSV was not associated with saphenous nerve injury.

Previous experience with EVLA indicated that some 44% of patients require delayed foam sclerotherapy for residual varicosities following ablation of the above-knee GSV. The greater proportion (61%) of limbs requiring sclerotherapy following standard EVLA in this study is explained by the presence of both above and below-knee GSV reflux in all limbs and mirrors the findings of Monahan who reported a similar rate of residual varicosities following GSV radiofrequency ablation (Monahan. 2005). Clearly, although ablation of the above-knee GSV will abolish SFJ and proximal GSV reflux, it only abolished reflux in the below-knee GSV in half of the limbs. In the presence of persistent reflux varicosities that connect directly to the below-knee GSV will almost certainly remain. Conversely, ablation of both the above and below-knee GSV should disconnect most if not all of the varicosities from the truncal vein and

thus ablation of the GSV from mid calf to groin is more likely control the varicose veins. In limbs where this was achieved by EVLA only 17% required subsequent sclerotherapy.

Group C received catheter directed foam sclerotherapy to the BK-GSV while Group A received delayed foam sclerotherapy at 6 weeks under ultrasound guidance via a cannula for their residual incompetent BK-GSV. The effectiveness of such ultrasound guided foam sclerotherapy is therefore not comparable to that of catheter directed foam sclerotherapy treatment.

This study has also shown that concomitant catheter guided below-knee GSV foam sclerotherapy following above-knee laser ablation was successful in abolishing GSV reflux 19/22 (86%) and reduced the requirement for subsequent sclerotherapy (36%) although this technique was not as effective as full length EVLA. The failure of chemical ablation in 3 patients in this group might be explained by the use of 1% STD rather than 3% STD. Nevertheless previous reports indicate that GSV ablation with STD foam is unsuccessful in about 10% of patients (Frullini et al. 2002; Jia et al., 2007). Although 2 patients in group C developed symptomatic phlebitis, the combination of sclerotherapy and thermal ablation is otherwise safe and more effective than standard above-knee EVLA alone. In addition to reducing the subsequent requirement for treating residual varicosities it was also accompanied by a greater improvement in the AVVS.

The frequency of skin staining following sclerotherapy to either the BK-GSV or to residual varicosities was relatively high. Although this has only been assessed at 12 weeks, and may have subsequently improved, it provides further justification for laser ablation of both the above and below-knee GSV when this is incompetent and technically feasible.

Although some 85% of limbs with primary varicose veins due to SFJ/GSV reflux are suitable for standard above-knee EVLA (Theivacumar et al., 2007), only 70% (67/95) with below-knee GSV reflux were suitable for longer length EVLA from mid-calf to groin because of below-

knee GSV tortuosity (fig 5.1). In these patients concomitant above-knee EVLA and below-knee foam sclerotherapy would seem to offer the most effective initial therapy.

Following above-knee EVLA persistent reflux in the below-knee GSV was successfully treated by DUS guided foam sclerotherapy and this explains the greater improvement in AVVS in group A between 6 and 12 weeks. Although this might be partly explained on the basis that these patients had more residual varicosities that were subsequently ablated by foam sclerotherapy they also had persisting BK-GSV reflux prior to further treatment. Recalculation of AVVS for group A at 6 and 12 weeks after excluding the scores representing the extent of the residual varicosities confirms that the improvement during this period remained significant and thus reflects the symptomatic benefit of abolishing BK-GSV reflux (Table 5.6).

The impact of persistent below-knee reflux upon symptoms has been described earlier and was the rationale for designing this trial. However, we have also shown that foam sclerotherapy directed only at the residual varicosities did not provide additional symptom relief following successful ablation of above-knee EVLA (Theivacumar et al., 2006). The findings of these studies suggest that when residual varicosities are associated with below-knee GSV reflux following standard EVLA further treatment should be directed at the below-knee GSV rather than the varicosities themselves. More importantly, this would suggest that above-knee EVLA combined with multiple phlebectomies may not be as effective as some suggest (Mekako et al., 2006) when below-knee GSV reflux is present. Further this technique may require the use of an operating theatre and perhaps general anaesthesia, thus reducing the cost-effectiveness of EVLA.

It is also clear that concomitant phlebectomy results in the excision of some varicosities that would have resolved spontaneously following abolition of GSV reflux, particularly in Group B patients, only 17% of whom required delayed sclerotherapy. Such a policy of delayed

intervention for persistent varicose veins is also promoted by Welch following RFA (Welch, 2006).

Although the presence of residual varicosities has been used as one of the end-points of this study it should be considered that following abolition of below-knee GSV reflux, the residual varicosities are unlikely to be responsible for symptoms. Thus their further treatment with sclerotherapy is only of cosmetic value. When such intervention is offered the risk of pigmentation, the frequency of which has been reported as 0-67% (Jia et al., 2007), must be discussed with the patient. Nevertheless pigmentation diminishes with time and Georgiev has reported that it persists in only 1% of patients at 1 year (Georgiev, 1990).

Although pigmentation may be cited as a reason for preferring phlebectomy over delayed sclerotherapy de Roos et al compared outcomes for the two techniques in a randomised controlled trial and reported that phlebectomies take longer and are associated with more complications [blisters, bruising, phlebitis, matting, scarring] (de Roos et al., 2003). Similarly, Brethauer et al who compared a policy of concomitant phlebectomy or delayed sclerotherapy described equivalent outcomes in terms of patient satisfaction but with a greater incidence of phlebitis in the phlebectomy patients (Brethauer et al., 2001). Finally Darwood et al have reported that there were no differences between the two techniques in terms of cosmesis with 95-98% of patients being satisfied with the outcome (Darwood et al., 2008).

This last point is important since it is often suggested that sclerotherapy is more likely to result in an unsatisfactory outcome because of associated pigmentation. However this complication also occurs after phlebectomy. Table 5.7 summarises data from a number of studies reporting the adverse events associated with these two therapies (Ramelet, 1997; de Roos et al., 2002; Frullini et al., 2002). For post-sclerotherapy pigmentation the data has been published by Georgiev who reviewed patients one year after their initial treatment (Georgiev, 1990).

	Phlebectomy	Sclerotherapy
Major haematoma	0.1-2-4%	N/A
Post-op haemorrhage	0.3-4.3%	N/A
Pigmentation	0.4-17.5%	5-25% (1%)*
Scars/skin necrosis	3-5%	0.2-1.0%
Phlebitis	0.4-20%	1.1-3.3%
Matting	0.5-9%	3-10%
Lymphocele	0.1-2.3%	N/A
DVT	0-0.5%	0.1-0.2%

Table 5.7: Complications of phlebectomy and sclerotherapy (N/A = not applicable)

*** proportion of patients with pigmentation at 1 year**

A potential drawback to performing EVLA from mid-calf to groin is the greater time required for the procedure. This largely relates to the administration of the tumescent anaesthesia. Compared to the standard technique treatment times for patients in groups B and C were an average of 5-10 minutes longer. It might also be considered that the risk of thermal injury to the saphenous nerve might be greater following below-knee EVLA because of the more intimate relationship of the nerve to the vein. This study provides no evidence to support this hypothesis.

Given that this study supports the concept that varicosities that are directly connected to a refluxing truncal vein will improve after ablation of the truncal vein, provided that the point of

communication is interrupted, it is logical to suggest that an incompetent truncal vein should be ablated from a point at or below the lowest point of branch reflux (Figure 5.2). This will require cannulation of a segment of competent truncal vein that will be of smaller diameter than the incompetent proximal vein. Whilst more experienced clinicians may find this relatively easy, this procedure can be facilitated by cannulating the vein with an 18G intravenous catheter which is smaller than the 5F needle supplied with the laser fibre, but still allows insertion of the guidewire. Similarly, most of the manufacturers of laser equipment include micro-puncture kits amongst their products. Alternatively the vein can be hooked to the skin surface through a small stab incision and cannulated under direct vision.

Although patients in group B had a higher satisfaction rate compared to the other 2 groups, this difference was not statistically significant. Similarly there was no difference in mean pain scores during the first week indicating that the 3 treatment methods are equally acceptable to patients.

In conclusion, longer length laser ablation of the great saphenous vein from mid-calf (or below the lowest point of reflux) to groin is safe and more effective than standard AK-GSV ablation when treating patients with below-knee varicose veins due to reflux in both the above and below-knee segments of the GSV. Although the follow-up in this study is short and does not provide any new data on the long-term efficacy of EVLA it seems logical that this technique should be adopted whenever possible. Alternatively, standard EVLA can be combined with catheter guided foam sclerotherapy to the below-knee GSV and this method would seem to offer the optimum therapy when tortuosity of the below-knee GSV makes it unsuitable for EVLA.

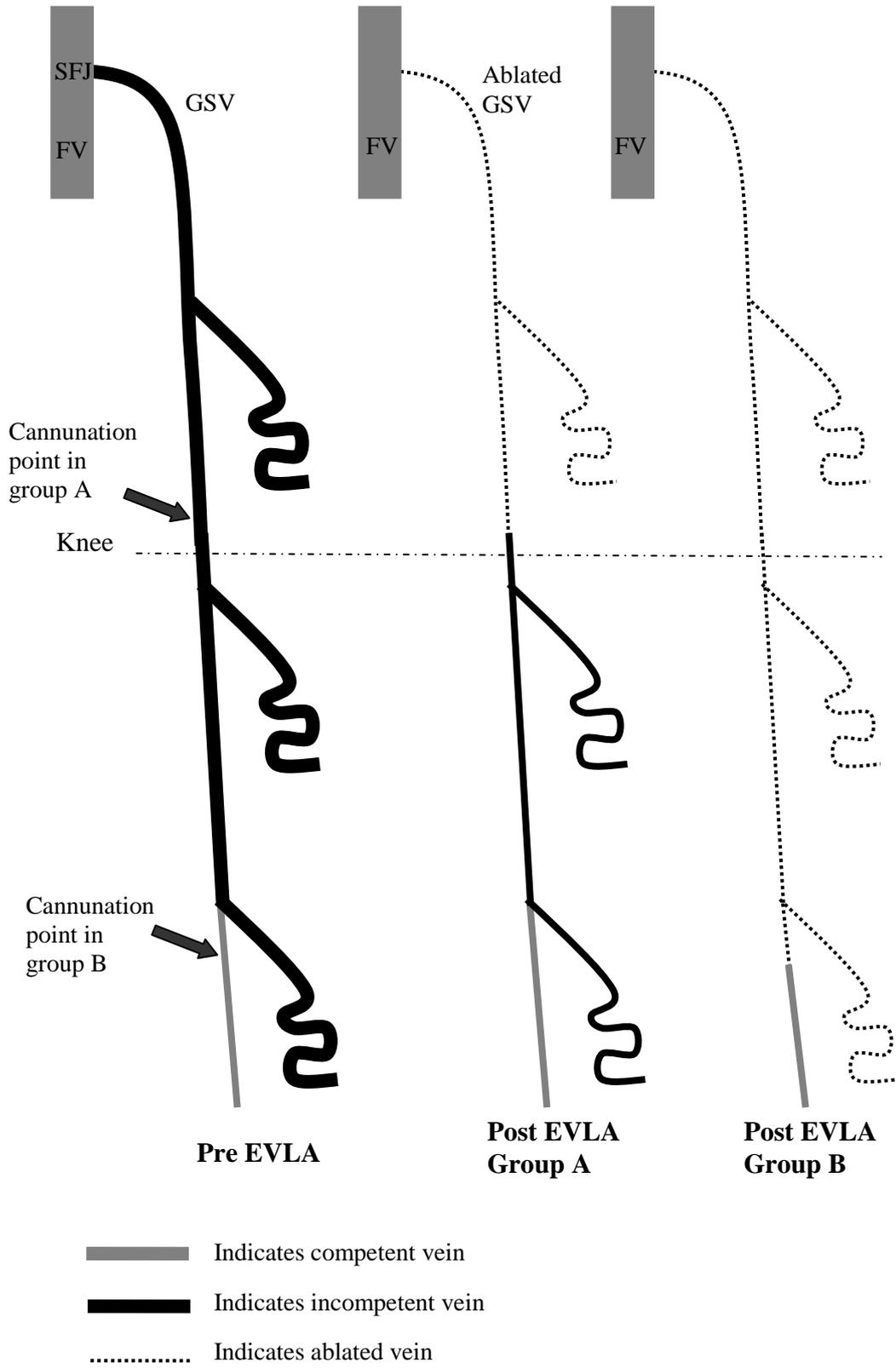


Figure 5.2: Shows the fate of varicosities following ablation from different points

Chapter 6:

6. Other applications for EVLA

EVLA was initially described as a method of treating GSV related varicosities (Min et al. 2001) and surgeons were reluctant to apply this technique to patients with SPJ/SSV reflux because of the close proximity between the high temperature laser fibre and the tibial nerve in popliteal fossa and the sural nerve in calf. However, previous work in our unit showed that the maximum temperature reached adjacent to the GSV during EVLA was 43.3°C, with a median maximum temperature of 34.5°C 3mm from the GSV (Beale et al., 2006). This is lower than the temperature that would be expected to cause permanent thermal neuronal injury (either by direct neuronal injury or by thrombosis of vasa nervorum causing neuronal ischaemia). Thus adjacent nerves should be safe during EVLA provided adequate tumescent anaesthesia is given to separate the nerves from the target vein. This chapter analyses the wider use of EVLA in the following situations:

1. Small saphenous vein (SSV) reflux
2. Anterior accessory great saphenous vein (AAGSV) reflux
3. Recurrent varicose veins
4. Paradoxical reflux

6.1 EVLA for small saphenous vein reflux

6.1.1 Introduction

The standard treatment for varicose veins associated with short saphenous reflux is ligation of the sapheno-popliteal junction (SPJ) with or without stripping of the small saphenous vein (SSV) under general anaesthesia. However recurrence rate following surgery may be as high as 50% at 3 years (van Rij et al., 2003). In many instances this is the result of inaccurate ligation of the SPJ. In addition neovascularisation, which is the commonest cause for recurrence following sapheno-femoral ligation and stripping, may have a role (Jones et al., 1996; van Rij et al., 2004). The frequency with which this occurs following SSV surgery has not been investigated but when present it allows further reflux into the SSV, which is often still present.

It has been suggested that the laser energy creates steam bubbles from blood which cause thermal injury to the vein wall resulting in damage to the endothelial and sub-endothelial tissues (Proebstle et al., 2002). Alternatively direct contact between the laser fibre and the vein wall may be responsible for the thermal injury. Aside from its anaesthetic function the tumescent anaesthesia absorbs heat and prevents injury to the surrounding tissues. Further it compresses the vein around the laser fibre. Although the temperature at the laser fibre tip exceeds 720⁰ C the impact of this on reducing peri-venous temperature has been described above. That EVLA may provide a more effective treatment for SPJ and SSV reflux is suggested by the poor results from surgery, the accurate visualisation of the SPJ with ultrasound during EVLA, allowing ablation of the SSV from this point distally, and the possibility that laser ablation reduces the risk of neovascularisation.

6.1.2 Methods

Patients

Of the 91 patients attending the venous clinics at the General Infirmary at Leeds between November 2004 and January 2006 with symptomatic varicosities due to SPJ/SSV reflux 65 patients (68 limbs) were found to be suitable for EVLA and underwent SSV EVLA. Suitability for the procedure depended upon a ≥ 10 cm relatively straight segment of SSV immediately distal to the SPJ, an absence of significant varicose tributaries arising within 5 cm of the SPJ and a distal SSV of ≥ 3 mm diameter at the intended cannulation site. Demographic details are shown in table 6.1. Primary varicose veins were present in 52 limbs whilst previous SPJ ligation had been performed in 16 limbs. Using the CEAP classification, determined by a consultant vascular surgeon or an experienced surgical trainee, the maximum grading was C₂ in 46 patients, C₃ in 8, C₄ in 12 and C₅ in 2. All C₂ patients complained of aching and/or pruritus.

Laser technique

In these studies the SSV was cannulated in mid-calf or a little higher if there was a relatively short segment of straight SSV under ultrasound guidance. Current practice however is to gain access to the SSV at or below the lowest incompetent tributary wherever possible. A guidewire was passed proximally into the popliteal vein and a 5F catheter was positioned under ultrasound control 1 cm distal to the SPJ. Relatively larger volumes (compared to greater saphenous vein EVLA) of perivenous tumescent local anaesthesia (0.1% lignocaine, 150-200ml) were infiltrated along the vein under ultrasound guidance with a greater proportion (50-60 ml) of this used in the popliteal fossa to eliminate the possibility of thermal nerve injury. A bare tipped fibre was inserted via the catheter and gradually withdrawn so that 5-6 pulses of laser energy (810 nm diode laser, 12Watts power, 1 second pulses at 0.1 second intervals) were delivered / cm vein (60-72 Joules/cm).

Number patients (n)	65 (68 limbs)
Median age (range)	48 years (28-82)
Male: Female	22: 43
BMI, median (\pm IQR)	25.1 (22.4-28.3)
Vein diameter [*] , median (\pm IQR)	6.2 mm (5.1-7.6)
C ₂ Varicose veins	n=46 (68%)
C ₃ Oedema	n=8 (11.7%)
C ₄ Skin changes	n=12 (17.6%)
C ₅ Healed ulcer	n=2 (2.9%)
C ₆ Active ulcer	n=0
E _p Primary	n=68 (100%)
A _d Deep veins	n=0
A _s Superficial veins	n=68 (100%)
P _r Reflux	n=68 (100%)

Table 6.1: Patient demography and disease severity scores (maximum “C” score for each patient)

* : maximum diameter measured with patient standing

CEAP score : Clinical, Etiology, Anatomy, Pathology

Following treatment a non-stretch compression bandage was applied to the limb for 1 week followed by a class 2 support stocking for a further week. Patients were prescribed 50 mg diclofenac sodium tds for 3 days to reduce inflammatory changes in the SSV. Patients were encouraged to resume their normal daily activities (including work) as soon as possible.

Data collection and Follow-up

Pre-treatment data collection included clinical assessment of the varicose veins (CEAP clinical stage), completion of the AVVS questionnaire and measurement of maximum SSV diameter on standing. Details of the laser energy used and the length of vein treated were also recorded. Following treatment patients were asked to keep an analgesic diary for one week and underwent clinical and duplex scan assessments at 6 weeks, 3 months and 6 months to determine whether the SSV had been successfully ablated.

Specifically, ultrasound examination determined if the SSV remained visible and if it did its patency was assessed on the basis of compressibility and visible colour flow following a calf squeeze. If SSV flow was present reflux was assessed using both Doppler waveform analysis and colour flow imaging. Finally, the deep veins were examined for evidence of deep vein thrombosis.

Clinical examination at 6 weeks was used to assess the extent of any residual varicose veins. If these were of cosmetic concern they were treated by foam sclerotherapy (1.0% sodium tetradecyl sulphate, mixed 1:3 with air using a 3-way tap). At subsequent clinical review the development of recurrent varicosities was determined.

The AVVS questionnaire was repeated at 3 months. All data including the ultrasound findings were collected by a team of 2 consultant vascular surgeons and 2 research fellows who had appropriate ultrasound training.

A prospective log of complications (thrombophlebitis, bruising, pigmentation, skin burn, DVT) was maintained and the presence of cutaneous numbness determined by direct questioning. If present this was mapped by clinical examination. Finally patients were asked whether they would undergo EVLA again and if they would recommend the procedure to a friend.

The AVVS before and after laser ablation were compared using a Wilcoxon test. A p value of <0.05 was considered significant.

6.1.3 Results

A median of 17cm (IQR: 12-20) of SSV was ablated using a total energy of 1131 J (IQR: 928-1364) delivered at an energy density of 66.3 Joules/cm (IQR 54.2-71.6).

The time taken return to normal daily activity was a median (IQR) of 0 (0-4) days with 42/65 (65%) patients doing so straightaway. The overall duration of analgesic use was 3 (0-14) days which may reflect the provision of a 3 day supply of diclofenac sodium (50mg tds). However 15/65 (23%) patients did not take any painkillers. 12/68 (18%) limbs received delayed foam sclerotherapy at 6 weeks for residual varicosities.

The median (IQR) pre-treatment AVVS was 15.4 (11.8-19.7) compared to 4.6 (3.2-6.7) 3-months post treatment (Figure 6.1). This improvement was highly significant ($p < 0.001$). Finally 64/65 (98%) patients would choose laser treatment again if they required it.

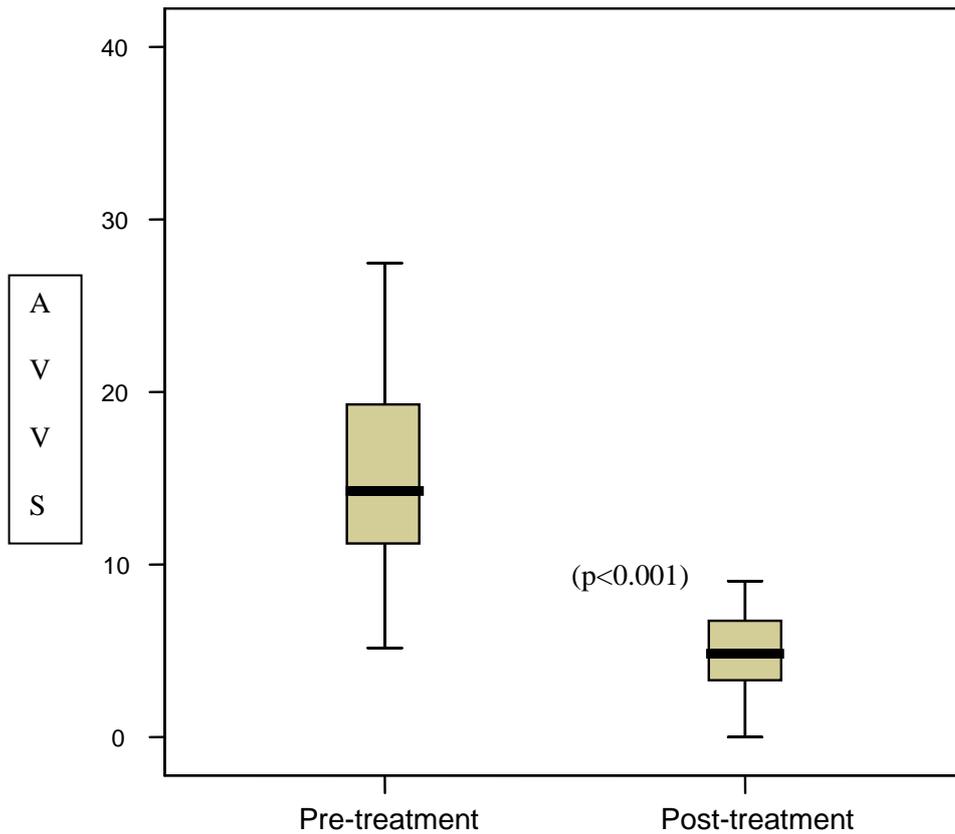


Figure 6.1: Pre and post treatment Aberdeen Varicose Vein Severity Scores (AVVS) in patients undergoing small saphenous vein laser ablation. Thick and thin horizontal lines indicate the median and range. The boxes represent inter quartile range

Although not specifically recorded, minor bruising along the line of the SSV was reported by most patients. However this had disappeared by the time of the 6-week assessment. Although some minor pigmentation was present in a minority of limbs at this time this had resolved in all patients by 3 months. No skin burns occurred.

Symptomatic superficial “phlebitis” of the SSV was documented in 3/68 (4.4%) limbs and was treated with a further course of diclofenac sodium 50 mg tds for as long as required. There was no evidence of deep vein thrombosis on either clinical or ultrasound examination in any patient.

Transient numbness in the distribution of the sural nerve was reported in 3/68 (4.4%) limbs at initial follow-up and this was confirmed by objective neurological examination. It resolved by 6 months in all patients. No other neurological symptoms or signs were documented.

Ultrasound examination confirmed complete occlusion of the small saphenous vein to the level of sapheno-popliteal junction in all limbs (68/68, 100%) at 6 and 12 weeks. Forty-eight limbs (46 patients) have completed at least six months follow up. The SSV was no longer visible in 42 limbs (87.5%), iso-echoic in 4 (representing simple occlusion) and hyperechoic (obliteration/fibrosis) in 2.

In the 12 limbs receiving sclerotherapy no further varicosities developed by 6 month follow-up and none of the patients (56 limbs) who did not require adjuvant sclerotherapy at 6 weeks have requested it to date.

6.1.4 Discussion

Successful treatment of small saphenous varicosities depends upon abolition of sapheno-popliteal and small saphenous vein reflux. The former is traditionally achieved by sapheno-popliteal ligation although stripping of the small saphenous vein is more controversial as it may be associated with sural nerve injury. Accurate ligation of the sapheno-popliteal junction can be technically demanding because of variability in its anatomical location and the relatively poor exposure of the popliteal vein and its branches afforded by a cosmetically acceptable incision. Although accurate ligation is facilitated by pre-operative ultrasound marking of the junction more than 50% of patients may develop recurrent varicose veins, often as a result of inadequate surgery (van Rij et al., 2003).

Conventional varicose vein surgery may also be associated with significant morbidity. Although usually minor (wound problems, cutaneous neuro-sensory loss) it may delay return to normal

activity and employment. Further, more serious complications may occur during saphenopopliteal ligation with 12 cases of foot drop due to nerve injury being recorded in the NHS Litigation Authority database in the period 1995-2003. Nevertheless one case of foot drop has now been described following SSV EVLA (Kumar and Gipinath, 2010).

In view of these drawbacks the newer minimally invasive methods of treating superficial venous incompetence in the SSV are of interest. The outcomes for both EVLA and RFA for GSV incompetence have been discussed earlier and thus the use of EVLA for SPJ and SSV reflux seems logical. Although efficacy for EVLA and RFA appear similar the UK cost of disposables for the latter is greater. Initially, a further advantage of EVLA was the shorter treatment times required compared to VNUS Closure (Covidien, Mansfield, USA) although this is no longer a factor following the introduction of VNUS ClosureFast.

Foam sclerotherapy of truncal veins is also gaining popularity and has the advantage of significantly lower cost. However there is some concern about the durability of the technique with GSV occlusion rates of 90% at 28 days but only 81% at 3 years (van den Bos, 2009). However, Darvall et al have recently reported a 91% success rate for SSV at 1 year (Darvall et al., 2009; Darvall et al., 2010). A further problem with the data for foam sclerotherapy is the lack of randomised controlled trials and thus the probability of reporting bias.

Unlike above-knee GSV ablation there was initial concern about the possible risk of nerve injury in the popliteal fossa during laser therapy for small saphenous vein reflux. However, despite the high temperature at the tip of the laser fibre a previous study from our unit which measured temperatures adjacent to the GSV confirmed that following adequate administration of tumescent anaesthesia the perivenous temperature reached a median of 34.5⁰C and thus nerve injury should be avoided (Beal et al., 2006).

The present study has confirmed that laser ablation of the small saphenous vein is both effective and safe. Although 3 patients developed temporary paraesthesia in the distribution of the sural nerve this resolved within 6 months. There was no evidence of other motor or sensory nerve injury. Similarly there were no instances of skin burns or other serious complications such as deep vein thrombosis. Further, the small saphenous vein was successfully ablated from the sapheno-popliteal junction in all patients with spontaneous regression of associated varicosities in the majority of patients (52/68 [76%]) limbs. In the 16 limbs with residual varicosities delayed (6 weeks) foam sclerotherapy was performed in 12 (18%). No further treatment was required in 4 limbs in which symptoms had resolved and any remaining varicose veins were of no concern. Successful ablation of the small saphenous vein was associated with a significant reduction in symptom severity scores and a rapid return to normal activity (65% of patients doing so immediately).

Although not the primary focus of this study the proportion of patients who were suitable for SSV EVLA was also assessed. Thus 50/69 (72%) and 15/22 (69%) of patients with either primary or recurrent varicose veins were suitable for EVLA.

Two other small studies have also reported similar results for SSV ablation (occlusion rates 95%, 97%) using EVLA (Proebstle et al., 2003; Perkowski et al., 2004), although neither reported the impact of this on symptom relief or the need for subsequent ambulatory phlebectomy or sclerotherapy. Similarly, post treatment morbidity was not described.

In summary, this study was the first to confirm the safety and efficacy of endovenous laser ablation in the treatment of small saphenous varicosities. Given the variable results of sapheno-popliteal ligation ultrasound guided laser treatment is likely to prove more successful than conventional surgery provided that the durability of the procedure is similar to that reported for GSV laser therapy.

6.2 EVLA of the anterior accessory great saphenous vein (AAGSV)

6.2.1 Introduction

Incompetence at the sapheno-femoral junction (SFJ) is the commonest cause [70%] (Labropoulos et al., 1994; Myers et al., 1995) of varicose veins and SFJ ligation and GSV stripping is the standard treatment for varicose veins associated with GSV reflux. In some patients reflux may occur in the anterior accessory great saphenous vein (AAGSV) rather than the GSV although many surgeons strip the latter when performing surgery for this type of incompetence. This study assesses the safety and short-term efficacy of AAGSV EVLA with preservation of a competent GSV in patients with isolated SFJ/AAGSV reflux.

6.2.2 Methods

Patients

Of the 474 patients who underwent laser treatment for their varicose veins between March 2004 and Jan 2007 at The General Infirmary at Leeds, 33 patients (median age of 43 (32-65), 21 female, 12 male) with isolated SFJ/AAGSV reflux (type A in figure 6.2) underwent AAGSV EVLA alone (group A). Twelve of these patients had undergone previous treatment for varicose veins [GSV EVLA (n=3); surgical stripping of GSV (n=9)]. Outcomes for patients in group A were compared with those for 33 age/sex matched controls who had GSV EVLA alone during the same time period (Group B: isolated SFJ/GSV reflux), 13 of whom had had previous treatment for varicose veins. Demographic data and the disease severity (CEAP classification) for the two groups are compared in table 6.2. Patients who had varicosities (primary or recurrent) arising from an incompetent SFJ with reflux in either the AAGSV (Group A) or GSV (group B) were included in the study but patients who had previous deep vein thrombosis (DVT) and those who with reflux in more than one truncal vein (AAGSV and GSV) were excluded. Further, limbs that had intra-saphenous reflux with a competent SFJ were also

excluded. Although types B and D in the figure 6.2 are also suitable for EVLA, they were not included in this study.

Characteristics	Group A	Group B
Number of patients (limbs)	33 (33)	33 (33)
Age	43 (32-65)	43 (32-65)
Male : Female	21:12	21:12
Primary: recurrent varicose veins	21:12	20:13
C2	28 (85%)	26 (79%)
C3	4 (12%)	5 (15%)
C4	1 (3%)	1 (3%)
C5/6	0	1 (3%)

Table 6.2: Patient demography and “C”: of CEAP classification for Group A (AAGSV reflux) and Group B (GSV reflux)

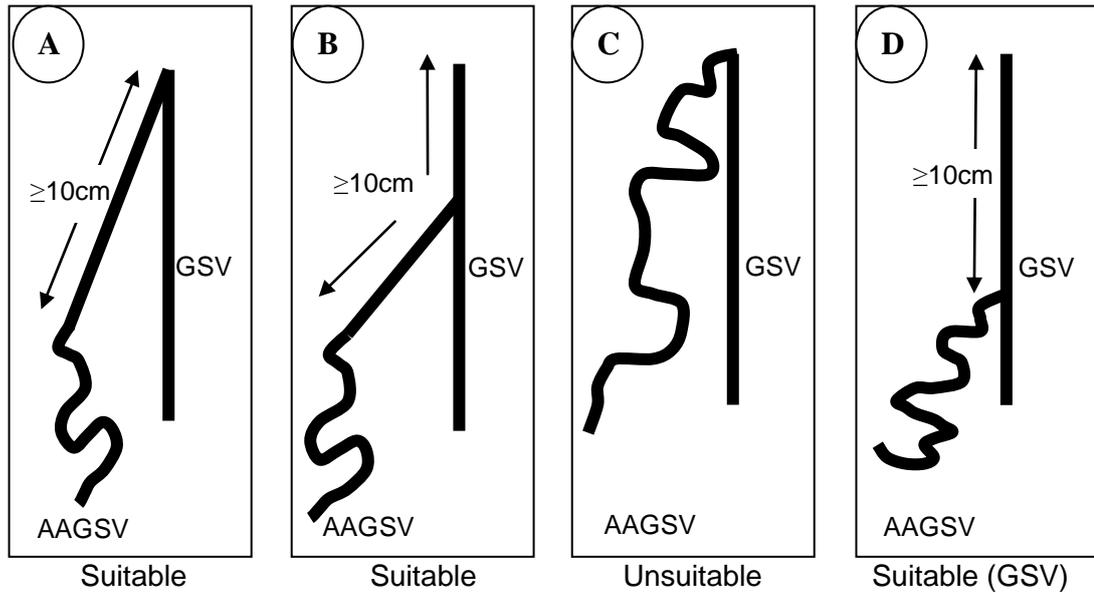


Figure 6.2: Laser suitability of different anatomical patterns of AAGSV reflux

EVLA technique

For group A, the AAGSV was cannulated as far distally as possible in the straight segment of vein under ultrasound guidance and a guidewire was passed proximally. A 5F catheter was positioned with the tip located at least 1 cm from SFJ to protect the competent GSV. In all other respects EVLA was performed as described in chapters 2 and 3 as it was for patients in group B.

Data collection and Follow-up

Prior to EVLA all patients underwent a duplex ultrasound scan (DUS) [TITAN®, Sonosite Inc, Bothell, USA, 5-10 MHz linear probe] to determine the site of superficial venous incompetence. Previous treatment for varicose veins was documented. Ultrasound examination was performed with the patient standing. Following calf compression and release retrograde flow in the truncal vein lasting >1 s represented significant reflux. The diameter of the GSV (10 cm distal to SFJ whilst standing, avoiding focal dilatations) was measured in both groups, as was the AAGSV diameter in group A. Suitability for GSV EVLA was established using criteria that have been described previously (chapters 2, 3). Similarly suitability for AAGSV EVLA depended upon a

≥ 10 cm relatively straight segment of AAGSV immediately distal to the SFJ, an absence of significant varicosities arising within 10 cm of the SFJ, and an AAGSV diameter of ≥ 3 mm at the intended cannulation site (Figure 6.3). Disease severity was assessed using “C” of the CEAP clinical classification⁴ prior to treatment (“EAP” of CEAP were the same for all patients) and the Aberdeen varicose vein severity score (AVVS) was determined before and 1 year after EVLA. All data were collected prospectively by a consultant vascular surgeon or vascular research fellow.

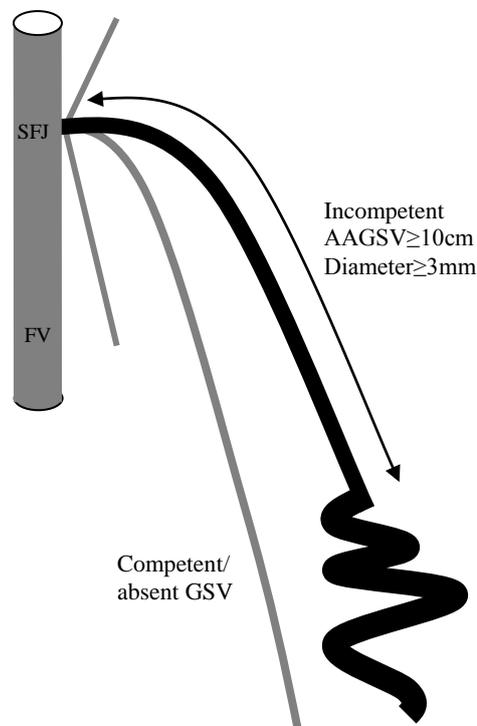


Figure 6.3: Suitability for EVLA in AAGSV in patients (Group A)

— Line represents a competent vein
 — Line represents an incompetent vein

FV: Femoral vein

SFJ: Sapheno-femoral Junction

GSV: Great saphenous vein

AAGSV: Anterior accessory GSV

EVLA was performed using tumescent local anaesthesia and an 810nm diode laser at 12W power delivering 60-80J/cm. Neither concomitant phlebectomies nor foam sclerotherapy were undertaken. Following treatment a compression bandage was applied for one week followed by a class II support stocking for a further week. Patients were reviewed at 6, 12 and 52 weeks. All patients with visible residual varicosities were treated with foam sclerotherapy at 6 weeks (if required) using 1% sodium tetradecyl sulphate (STD) foam (Fibro-vein®, STD Pharmaceutical Products Ltd, Hereford, England) prepared by the Tessari method (Tessari et al., 2001). A non-stretch compression bandage was applied for 1 week following foam sclerotherapy of residual varicosities.

During follow up, in addition to clinical examination for residual varicosities, assessment of symptom improvement (AVVS) and a record of complications DUS was also performed at 6, 12 and 52 weeks to assess SFJ and tributary competence and ablation or otherwise of the AAGSV. Patency of the deep veins was assessed at 6 and 12 weeks and the diameters of visible veins were re-measured at 1 year. Absence of flow in a non-compressible vein or a non-visible GSV or AAGSV vein on DUS represented successful ablation. The primary outcomes were DUS confirmed ablation rates and the improvement in AVVS in both groups at 1 year. Patient satisfaction was assessed at 1 year using a visual analogue scale of 1 to 10 on a 10 cm scale. Patients were asked to locate their satisfaction point on this scale which was then calculated as a percentage. A log of complications was maintained throughout the study. Secondary outcomes included patients' satisfaction, sclerotherapy requirement and complication rates. All data were collected prospectively.

Statistical analysis

AVVS scores before and after laser ablation were compared within a group using a Wilcoxon test and the improvements in AVVS between groups were compared by a Mann-Whitney U test. Sclerotherapy requirements were compared using a chi-square test. A p value of <0.05 was

considered significant. Data are presented as median (inter-quartile range) unless stated otherwise. All analysis were performed using the statistical package SPSS® for Windows (SPSS (14), Chicago, Illinois, USA).

6.2.3 Results

The treatment details for both groups are summarised in table 6.3. All treated anterior and great saphenous veins were completely ablated and SFJ reflux abolished in all patients of both groups at one year. Foam sclerotherapy for residual varicosities was required in 20/33 (61%) of group A and 14/33 (42%) of group B ($\chi^2 = 2.2$ (1 df) $p=0.218$). Patient satisfaction scores were similar (Group A: 84%, Group B: 90%, $p=0.23$) and the AVVS had improved at 1 year when compared to pre-treatment scores (A: 4.1 (2.1-5.2) v 11.6 (6.9-15.1); group B: 3.3(1.1-4.5) v 14.5 (7.6-20.2); $p<0.001$ for both groups. Percentage improvement in AVVS was 64.6% (Group A), and 77.2% (Group B) with no significant difference between the groups ($p=0.18$).

Parameters	Group A (AAGSV)	Group B (GSV)	p-value
Diameter of treated vein (mm)	7.1 (5.2-8.0)	7.8 (5.2-8.8)	0.12
Length of vein ablated (cm)	19 (14-24)	32 (24-42) cm	<0.001
Total laser energy (J)	1178 (912-1488)	2012 (1460-2466)	<0.001
Laser energy density (J/cm)	61 (56-68)	63 (57-68)	0.34

Table 6.3: Treatment details for Group A (AAGSV reflux) and Group B (GSV reflux)

None of the participants developed a DVT or signs of sensory nerve damage although 2 patients in group A and 1 in group B had symptoms of phlebitis in the EVLA-treated vein before sclerotherapy was performed. In addition, of 34 patients (from both groups) who received delayed foam sclerotherapy 5 (3 in group A and 2 in group B) developed symptomatic phlebitis. Although skin staining was not documented at 6 weeks, it was present in 11 patients following

foam sclerotherapy at 12 weeks. This had faded in all patients by 1 year but was still visible in 3/34 (9%) patients. No other complications occurred.

Twelve patients in group A had undergone previous GSV stripping or EVLA. In the remaining 21 patients the GSV was preserved following AAGSV ablation and all were in continuity with the SFJ with no evidence of reflux at 1 year. Similarly, the GSV diameter remained unchanged (3.2 ± 0.9 (pre-treatment) versus 3.3 ± 0.6 (1 year); $p=0.32$). A similar improvement in AVVS scores was also observed in this sub-group (4.4 (2.0-5.4) v 11.4 (6.0-14.1), $p=0.002$) Finally, the AAGSV was non-visible on DUS at 1 year in any patient in Group A and no clinical recurrences were visible in patients from either group at this review

6.2.4 Discussion

Abolition of SFJ reflux requires ablation of all incompetent truncal veins arising from the junction. Thus AAGSV ablation abolishes reflux at the SFJ when associated with isolated reflux in this vein. Figure 6.4 illustrates the fate of the SFJ, GSV and AAGSV following successful AAGSV ablation. The subsequent improvement in symptom scores was similar to that achieved after GSV ablation.

Although SFJ reflux can be associated with incompetence in one or more of its tributaries, most patients (85%) only have GSV reflux (Theivacumar et al., 2007) and GSV ablation abolishes SFJ reflux with persisting competence of its tributaries at 1 year (chapter 4.2). Equally, when SFJ incompetence is associated with reflux in more than one truncal vein (5%; Theivacumar et al., 2007), all incompetent veins require either ablation (EVLA) or stripping (surgery) to restore SFJ competency.

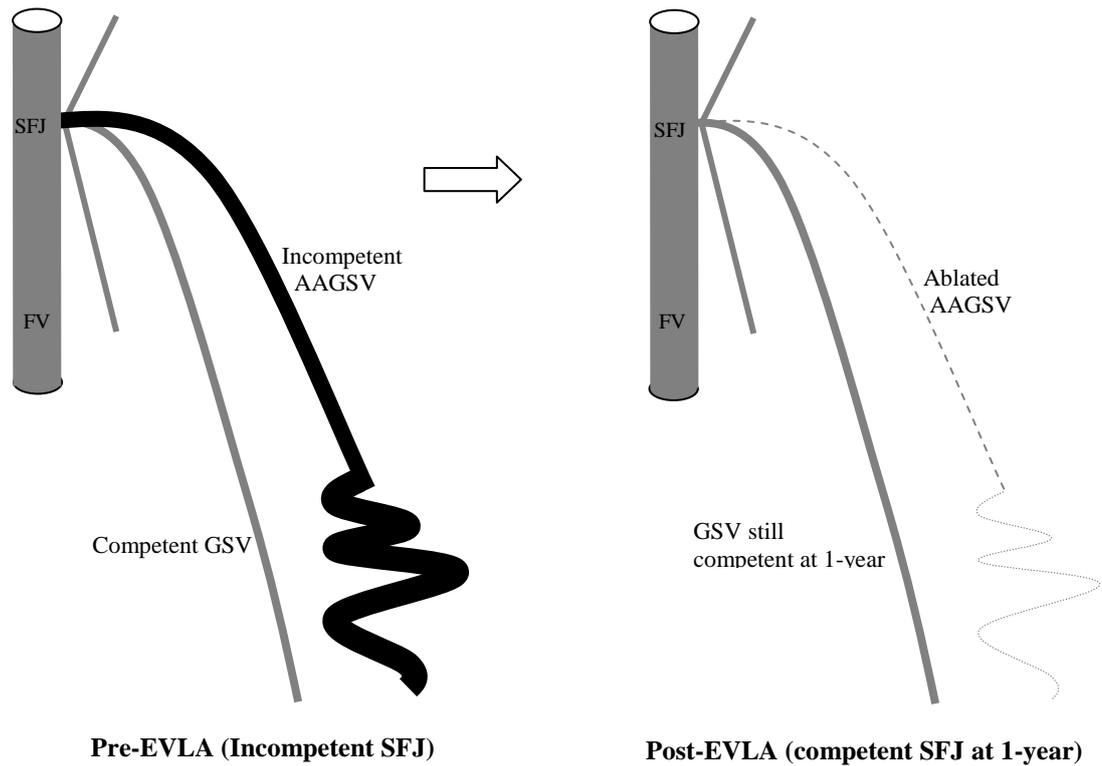


Figure 6.4: Diagrammatic representation of GSV-sparing AAGSV laser ablation

— Line represents a competent vein
 — Line represents an incompetent vein

FV: Femoral vein

GSV: Great saphenous vein

SFJ: Sapheno-femoral junction

ASSV: Anterior accessory saphenous vein

Isolated AAGSV/SFJ reflux occurs in around 10% of the patients (Theivacumar et al., 2007). During conventional surgery many surgeons also strip the competent GSV because of the possibility that post-SFJ ligation neo-vascularisation may subsequently promote GSV reflux and recurrent varicose veins. Although stripping of incompetent truncal veins is required to reduce recurrence rates there is no evidence to support this for competent veins. During EVLA selective ablation of the incompetent truncal vein can be achieved without the need to ablate competent truncal veins. Thus a healthy GSV may be preserved. Subsequently it will still be available if required for vascular or coronary artery reconstruction. That such a policy is likely to be successful is further supported by the finding that EVLA is believed to be associated with

a lower risk of neovascularisation (Chapter 7) presumably because there is less trauma to the surrounding tissue.

Ideally, AAGSV EVLA should have been compared with surgery for AAGSV reflux. The issue of routine practice for this type of reflux (in the UK) made this difficult. Further, most patients with varicose veins now chose EVLA over surgery if their truncal veins are suitable for ablation. Nevertheless, comparing AAGSV and GSV EVLA in this study suggests that symptom improvement is similar. Further, previous studies show that EVLA and surgery in patients with SFJ/GSV reflux (Mekako et al., 2006; Darwood et al., 2008; Carradice et al., 2011) are equally effective in improving symptom scores.

Despite these results, EVLA is unlikely to replace surgery for all patients with SFJ/AAGSV reflux as anatomical considerations (figure 6.2) mean that it is only feasible in 70% of cases (unpublished data). Although not statistically significant (small sample size), the sclerotherapy requirement was higher following AAGSV EVLA compared to GSV EVLA. This reflects the shorter segment of AAGSV that can be ablated, and the extensive varicosities that may be present distal to the site of vein cannulation. This is consistent with previous findings that the need for adjuvant sclerotherapy is minimised by commencing ablation at the lowest point of reflux (chapter 5).

Following GSV EVLA some 40% of patients do not have any branch tributaries in continuity with the SFJ (chapter 4.2). In contrast following AAGSV EVLA the GSV remains in continuity with the SFJ in all patients allowing normal GSV function. In conclusion, GSV sparing EVLA of the AAGSV abolishes SFJ reflux associated with isolated SFJ/AAGSV incompetence, and improves symptom scores to a similar degree as GSV EVLA with no evidence of GSV neo-reflux, or recurrent varicosities at 1 year. This treatment option preserves the healthy GSV for future use if required. Although long-term results are required, the technique appears both safe and effective.

6.3 EVLA for recurrent varicose veins

6.3.1 Introduction

Recurrence following surgical treatment of varicose veins is common particularly when follow-up is extended to 10 years or more (Campbell et al., 2003, Winterborn et al. 2004a). Thus some 20% of the patients requiring treatment for varicose veins have recurrent varicosities (Dark, 1992) following surgery for either SFJ/GSV or SPJ/SSV reflux. Whilst many authors have associated recurrence with the development of either junctional or strip-tract neo-vascularisation (Jones et al., 1996) others believe that technically inadequate surgery may have an important role, particularly following sapheno-popliteal ligation. Other reasons for the development of recurrent varicose veins also include perforator incompetence and undiagnosed pelvic vein reflux (Egan et al 2006, van Rij et al., 2005; Blomgren et al., 2005).

Re-do surgical treatment is time consuming and technically challenging and is associated with more complications (Loeprecht, 1997; Earnshaw et al., 1999; Perrin et al., 2000). It therefore seems logical to consider the safety and effectiveness of endovenous laser ablation (EVLA) in the treatment of these where it is appropriate. This may particularly be the case when the incompetent truncal vein remains in-situ (not stripped, incomplete stripping) at the previous surgery. Further information is provided below in respect of the suitability of patients for EVLA for recurrent varicose veins arising from an incompetent GSV, AAGSV or SSV.

6.3.2 Methods

Patients

Patients attending the venous clinic at The General Infirmary at Leeds with a history of recurrent varicose veins were assessed both clinically using the CEAP classification and by duplex ultrasound scan (DUS), (TITAN®, Sonosite Inc, Bothell, USA). This was performed to

assess the suitability for EVLA. When confirmed patients were offered EVLA in preference to conventional surgery. Consecutive patients who have undergone EVLA for their recurrent varicose veins between March 2005 and March 2007 were included in this study. Varicosities due to at the sapheno-popliteal reflux following previous groin surgery and those due to sapheno-femoral incompetence after sapheno-popliteal ligation were not included in this study.

During the study period 106 limbs in 91 consecutive patients (male: 31 female: 60, median age 56 [iqr 42-74]) who underwent EVLA for their recurrent varicose veins and completed at least 12-weeks follow up by August 2007 were included in the study. Those who had recurrence secondary to isolated GSV incompetence (Group Gr: 51 limbs in 47 patients) were compared with an age and sex matched group of patient undergoing EVLA for primary SFJ/GSV reflux (Group Gp). The controls were identified from the prospectively maintained database with same age (± 2 years), sex and disease severity matched individuals. Similarly those who had recurrence arising from an isolated incompetent residual SSV (Group Sr: 24 limbs in 23 patients) were compared with a matched group of patients who had EVLA for primary SPJ/SSV reflux (Group Sp).

Suitability of recurrent varicose veins for EVLA

All recurrent varicose veins that are associated with an incompetent relatively straight segment of truncal vein (GSV/AAGSV/SSV) which measures >10 cm in length and >3 mm in diameter at the intended cannulation site were considered as potentially suitable for EVLA provided that the varicosities were arising from this vein. The presence of junctional neovascularisation did not precluded EVLA. Conversely, varicosities that connected directly to the neo-vessels, or that were secondary to either perforating or pelvic vein reflux without an interim truncal vein were considered unsuitable for EVLA. Figure 6.5 illustrates types of recurrences and their suitability for EVLA.

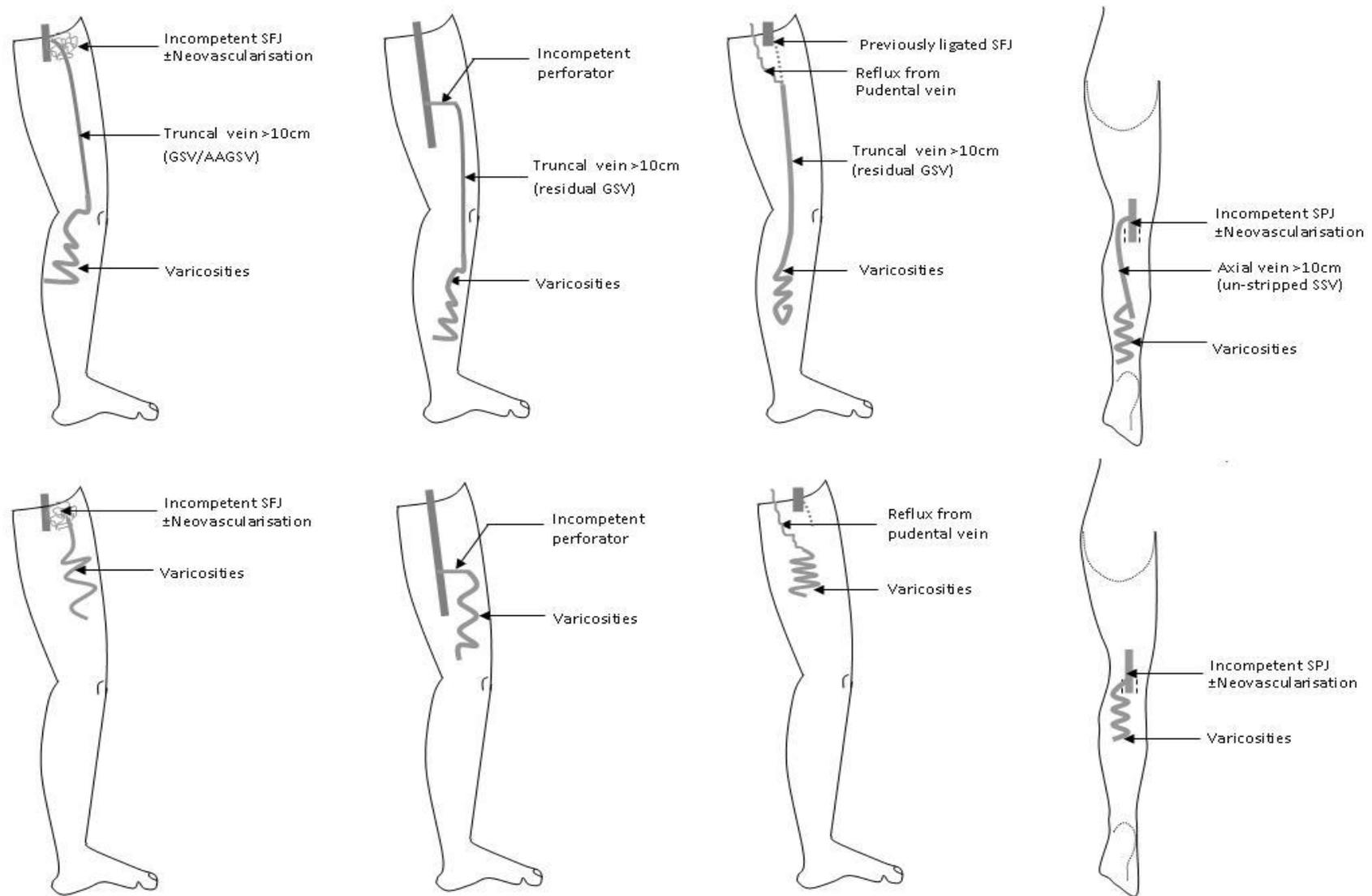


Figure 6.5: Patterns of recurrent varicose veins and their laser suitability (upper row veins are suitable for EVLA while the lower row veins are not)

EVLA technique

The target truncal vein (residual GSV or SSV) was treated by endovenous application of laser energy using an 810 nm diode laser at 12W power under tumescent local anaesthesia (0.1% Lignocaine) as an out-patient procedure. Full detail of the EVLA technique is described earlier in this thesis (chapter 2). The guidewire usually (but not always) failed to enter the common femoral or popliteal veins after previous GSV/SSV ligation and thus the sheath was advanced as far as possible without piercing the vein wall. The tip of the sheath was visualised by DUS to confirm its position within the appropriate superficial vein. In patients in whom the truncal vein was connected to a deep vein via neovascularisation, these were filled with 1-2 ml of sclerosant foamed (3% sodium tetradecyl sulphate [STD], [Fibro-vein®, STD Pharmaceutical Products Ltd, Hereford, England]) prepared according to Tessari's method. The foam was administered via the endovenous catheter (ELVeS™ Plus Katheter; Biolitec Group, Bonn, Germany) prior to the introduction of the laser fibre. However as routine foam sclerotherapy was not used to treat other superficial varicosities at the initial treatment. Following EVLA a compression bandage was applied for 1 week followed by a grade 2 compression stocking for a further week. Residual varicosities were treated by delayed foam sclerotherapy at 6-12 weeks.

Data collection

In all patients, disease severity was assessed using CEAP, VCSS and AVVS. Treatment details including the length of vein ablated, the laser energy delivered, and the requirement for junctional sclerotherapy to neo-vessels were all recorded prospectively. The control group was obtained from the Leeds EVLA database.

Following treatment patients were reviewed at 6, 12 and 52 weeks with a median [iqr] follow up of 12 months (3-18 months). The abolition or persistence of deep to superficial reflux and truncal vein incompetence were recorded together with the requirement for sclerotherapy for

persistent residual superficial varicosities. Post treatment clinical severity was determined using VCSS and AVVS. Finally a log of complications was maintained throughout the study.

Statistical analysis

The VCSS and AVVS before and after laser ablation were compared within a group using a Wilcoxon test and the improvements in AVVS between groups were compared by a Mann-Whitney U test. A p value of <0.05 was considered significant. Data are presented as median (\pm inter-quartile range) unless stated otherwise. All analysis were performed using the statistical package SPSS® for Windows (SPSS (14), Chicago, Illinois, USA).

6.3.3 Results

The type of recurrence is shown in table 6.4 and patients' demographic details for each of the groups are given in table 6.5.

Reason for recurrence	Group	n	%
Recurrent GSV \pm groin neovascularisation	Gr	51	48%
Para-reflux into AAGSV \pm groin neovascularisation		11	10%
Residual GSV supported by reflux from pudendal vein		4	4%
Incompetent thigh perforator with distal GSV reflux		6	6%
Recurrent SSV reflux \pm popliteal neovascularisation	Sr	24	23%
> 1 source of reflux (combinations of above)		10	9%
Total		106	100%

Table 6.4: Anatomical causes of recurrent varicose veins treated by EVLA

	Group Gr (Recurrent GSV)	Group Gp (Primary GSV)	Group Sr (Recurrent SSV)	Group Sp (Primary SSV)
Number of patients (limbs)	47 (51)	47 (51)	23 (24)	23 (24)
Age median (iqr)	52 (42-68)	52 (42-68)	49 (33-65)	49 (33-65)
Male : Female	20:27	20:27	9:14	9:14
C2 of CEAP	27 (53%)	30 (59%)	10 (42%)	11 (46%)
C3 of CEAP	9 (17.6%)	7 (14%)	7 (29%)	8 (33%)
C4 of CEAP	10 (19.6%)	11 (21%)	5 (21%)	4 (17%)
C5/6 of CEAP	5 (9.8%)	3 (6%)	2 (8%)	1 (4%)
VCSS	4 (3-5)	4 (3-5)	4 (3-5)	4 (3-5)

Table 6.5: Patients' demography and CEAP/VCSS scores of the age and sex matched study groups

Groups Gr & Gp

Data on the length of vein ablated, vein diameter and laser energy used is shown in table 6.6.

The GSV was ablated in 49/51 (96%) limbs in Group Gr whilst 2 veins had partially recanalised by 3 months. In Group Gp 50/51 (98%) veins were successfully treated. The AVVS score improved from 14.2 (10.2-18.9) to 3.2(1.2-6.4), $p<0.001$ in Group Gr and from 15.9 (11.4-22.7) to 3.8 (1.1-5.6), $p<0.001$ in Group Gp. The % improvement in AVVS was 78 % and 76% in groups Gr and Gp respectively ($p=0.23$). Delayed foam sclerotherapy was required in 19/51 (37%) limbs in Group Gr and in 20/51 (39%, $p=0.5$) in Group Gp:. Three and 5 patients developed symptoms and signs of post-EVLA phlebitis in groups Gr and Gp respectively

($p=0.36$) and patient satisfaction was similar in both groups Gr-86%, Gp-82% ($p=0.32$). Although neovascularisation was treated with foam sclerotherapy in 24 limbs in Group Gr 19 still had evidence of persisting groin neovascularisation in the groin at 3 months. In this subgroup 23/24 GSVs were completely ablated and this was associated with a significant improvement in AVVS from 13.6 (8.5-17.7) to 2.1 (0.5-4.3), $p<0.001$, at 12 weeks. The clinical severity of the varicose veins in these patients was also assessed by VCSS which improved from 4 (3-5) to 1 (0-2) and 4 (3-5) to 1 (0-2) in Gr and Gp respectively (table 6.7).

Groups Sr & Sp

Data on the length of vein ablated, vein diameter and laser energy used is shown in table 6.6.

The SSV was completely ablated in all 24 limbs in both groups and the AVVS improved from 14.4 (8.2-19.4) to 2.4 (1.9-4.6), $p<0.001$ in group Sr and from 13.8 (6.3-17.5) to 2.2 (1.2-5.1), $p<0.001$ in group Sp. The % improvement in AVVS was 83% and 84% respectively ($p=0.33$). Delayed foam sclerotherapy was required in 8/24 (33%) and 6/24 (25%), $p=0.38$ in groups Sr and Sp. Post-EVLA phlebitis occurred in 2 and 3 patients respectively ($p=0.5$) whilst patient satisfaction was again similar in both groups: Gr 88%, Gp 90% ($p=0.42$). The clinical severity of the varicose veins in these patients was also assessed by VCSS (table 6.7).

AAGSV

AAGSV reflux was successfully ablated in all 11 limbs and the AVVS improved from 13.4 (8.3-16.3) to 3.2 (1.7-4.9), $p<0.01$. Delayed foam sclerotherapy was required in 6/11 (54%) and patient satisfaction was 78%. No reported phlebitis occurred after EVLA although 2 patients had phlebitis after adjuvant foam sclerotherapy.

	Group Gr	Group Gp	P (Gr v Gp)	Group Sr	Group Sp	P (SR v SP)	AAGSV
Number of limbs	51	51	-	24	24	-	11
Total laser energy (J)	2116 (IQR 1392-2591)	1998 (IQR 1317-2580)	0.23	1286 (IQR 910-1520)	1254 (IQR 899-1498)	0.28	1360 (IQR 990-1642)
Energy Density (J/cm)	61 (IQR 52-66)	60 (IQR 52-64)	0.32	64 (IQR 55-69)	66 (IQR 56-71)	0.36	62 (57-66)
Diameter of the vein (mm)	7.6 (IQR 5.3-8.0)	7.7 (IQR 5.7-8.2)	0.41	7.4 (IQR 4.2-8.1)	7.2 (IQR 4.1-8.0)	0.29	6.3 (4.6-7.4)
Length of vein (cm)	36 (IQR 28-41)	34 (IQR 27-40)	0.21	20 (IQR 16-22)	19 (IQR 16-21)	0.43	22 (IQR 16-28)

Table 6.6: Treatment details and vein size for the study (GR, SR) and control (GP, SP) groups. (IQR: inter-quartile range)

Groups n=patients (limbs)	Pre treatment AVVS	1 yr post-EVLA AVVS	P*	% improvement AVVS		Pre EVLA VCSS	Post EVLA VCSS (1 year)
Gr n=42 (44)	14.2 (10.2-18.9)	2.1 (1.1-6.1)	<0.001	85	Gr v Gp p=0.32	4 (3-5)	1 (0-2)
Gp n=43 (43)	15.9(11.4-22.7)	2.8 (1.2-5.9)	<0.001	82		4 (3-5)	1 (0-2)
Sr n=20 (21)	14.4 (8.2-19.4)	2.2 (1.7-4.7)	<0.001	85	Sr v Sp p= 0.39	4 (3-5)	1 (0-2)
Sp n=22 (22)	13.8 (6.3-17.5)	2.0 (1.1-4.9)	<0.001	86		4 (3-5)	1 (0-2)
AAGSV n=8 (10)	13.4 (8.3-16.3)	3.2 (1.7-4.9)	<0.001	76		4 (2-5)	1 (0-2)
Perforator n=4 (4)	12.1 (6.9-14.5)	3.2 (2.1-6.4)	#	74		4 (2-5)	(0-2)

* Pre-EVLA versus Post-EVLA (1 year) AVVS

insufficient numbers to allow calculation of significance

Table 6.7: Comparison of AVVS and VCSS scores at 1 year

Incompetent perforators

Six patients with incompetent mid thigh perforators were also treated successfully and the perforating vein regained competency (unidirectional flow during distal calf compression and release) in all 6 patients following EVLA. A diagrammatic representation of such a perforating vein before and after EVLA is shown in figure 6.6. Two patients required delayed foam sclerotherapy for residual varicosities. As in the other study groups the AVVS improved from 12.1 (6.9-14.5) to 4.6 (2.1-6.6) at 3 months and to 3.2 (2.1-6.4) at one year. Patient satisfaction was 76%.

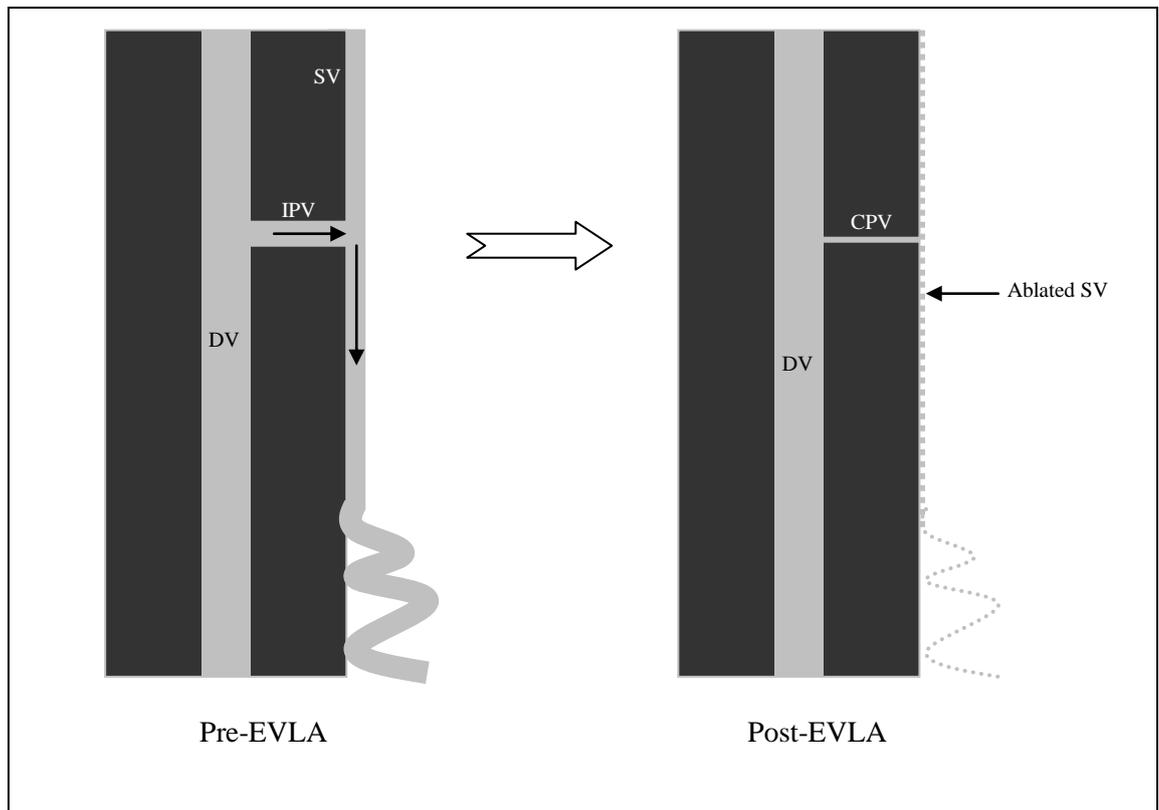


Figure 6.6: Diagram showing the fate of incompetent perforating veins after EVLA of the superficial truncal vein.

DV: Deep vein

IPV: Incompetent perforating vein

SV: Superficial vein

CPV: Competent perforating vein

Similarly all 4 GSV were successfully ablated in those who had residual GSV reflux supported by an incompetent external pudendal vein (Figure 6.7). The untreated pudendal vein tributary remained patent with minimal reflux (<1s). Only one patient required delayed foam sclerotherapy for residual varicose veins and the AVVS improved from 11.5 (8.9-14.1) to 3.5 (2.1-4.4) and patient satisfaction was 75%.

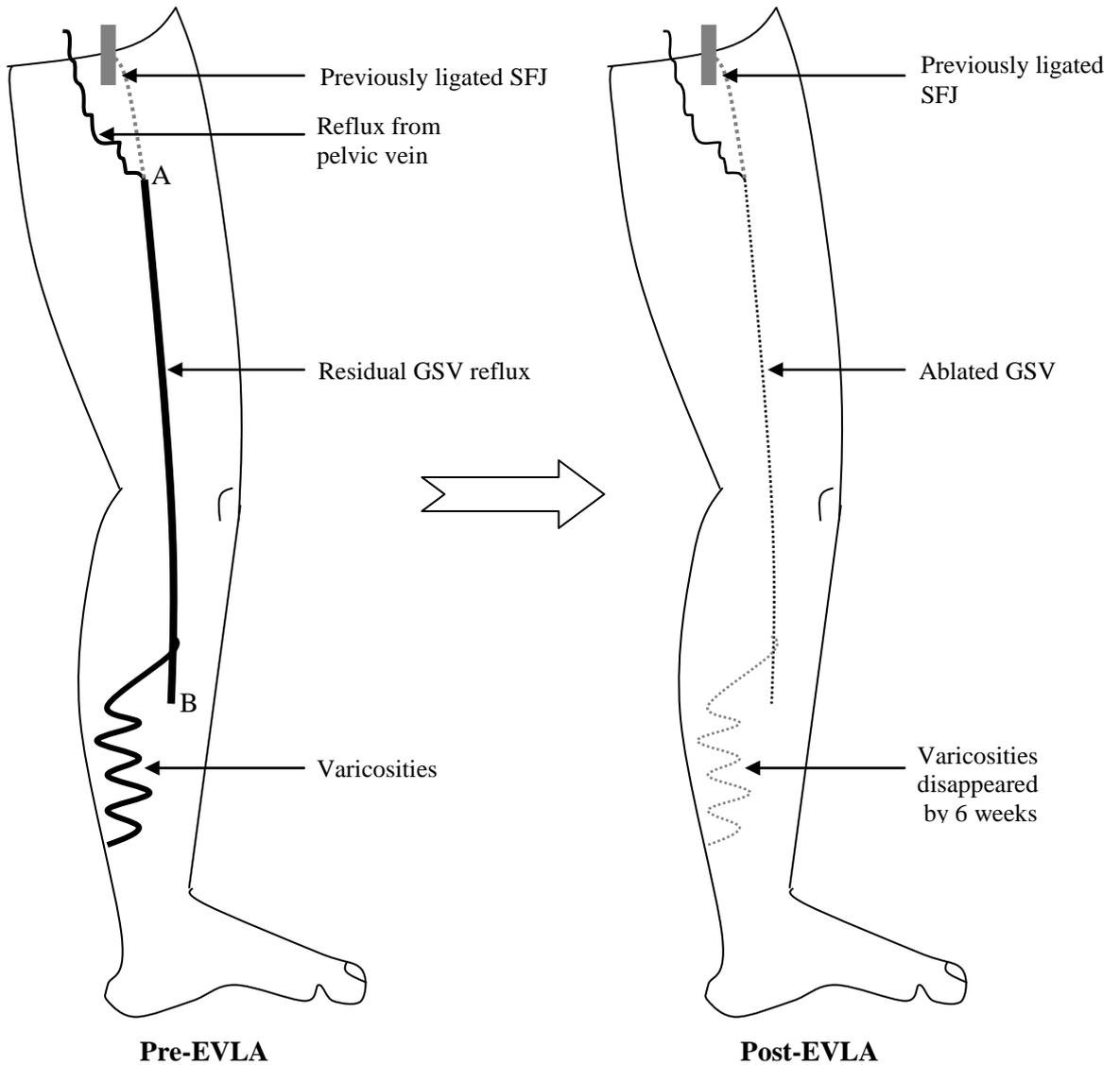


Figure 6.7: Diagrammatic representation of recurrent varicose veins due to reflux in a residual GSV supported by a pelvic vein. Truncal segment AB was ablated by laser treatment

No patients had evidence of deep vein thrombosis during follow up. Although 1 patient in group Sp had transient numbness in the distribution of the sural nerve this had resolved by 6 months. No other neurological symptoms were recorded in this study. The overall incidence of post-EVLA phlebitis was 8% (8/106) and this was treated with a 1-2 week course of diclofenac sodium 50 mg tds.

6.3.4 Discussion

Recurrence following varicose vein surgery is common after both sapheno-femoral and sapheno-popliteal ligation. Most recurrent varicose veins (65%) are due to reflux at the SFJ (Jiang et al., 1999) and this may result in reflux into a residual GSV or AAGSV.

Alternative causes of recurrent GSV reflux include an incompetent perforating vein in the thigh or proximal calf, or a residual GSV may establish a communication with veins that drain into pelvis, often via the perineum. For these routine re-exploration of groin would be unnecessary.

Recurrence following sapheno-popliteal surgery is relatively more common and occurs in up to 60% (Jiang et al., 1999) of patients after sapheno-popliteal ligation. The causes include failure to ligate the SPJ and the non-stripped SSV regaining a communication with the popliteal vein via neovascularisation. Rashid et al found that the former was the case in some 22% of patients despite preoperative DUS marking of the SPJ (Rashid et al., 2002). Re-exploration of the SPJ can be difficult and has rarely been associated with major nerve injury. Thus minimally invasive treatment is an attractive option.

Although GSV stripping is associated with lower recurrence rates (Dwerryhouse et al., 1999) in the absence of pre-operative ultrasound marking and quality control, which is rarely performed, Jiang et al in 1999 found that a residual GSV was present in 43% of the patients who had previously undergone high tie with GSV stripping. Similarly, in many patients with recurrent

GSV varicosities in this series it appeared as if the GSV had not been stripped despite the belief that it had. Whilst some of these patients may have had a duplex saphenous system the prevalence of this was not known in this series.

In the majority of patients with recurrent GSV reflux this was secondary to groin neovascularisation although a few had a relatively normal appearance to the SFJ on DUS when it appeared that the tributaries had been previously ligated but not the GSV. This is likely to reflect inadequate primary surgery.

In patients with groin neovascularisation attempts were made to obliterate the neo-vessels with STD foam administered via the laser catheter. Although ablation of all refluxing veins was rarely achieved (5/24) it is possible that the extent of reflux was reduced in some patients with persistent neo-vessels on follow up DUS and thus no re-recurrence or compromise in clinical outcome was documented due to persisting neovascularisation at 1 year. As the degree of neovascularisation was not formally measured in this study, it is not possible to comment further upon the effectiveness of foam sclerotherapy in the treatment of neovascularisation. Importantly however, there was no evidence of DVT following the use of foam sclerotherapy to treat neovascularisation. In respect of all other potential complications these were similar in both patients with primary varicose veins and those undergoing treatment for recurrence.

Although not employed in this study it might also be reasonable to employ catheter-directed foam sclerotherapy at the time of EVLA for GSV reflux which is originating from incompetent pelvic veins, particularly since these seemed to exhibit persistent (but reduced) reflux following EVLA.

In the UK SSV stripping is not routinely performed and thus most recurrent varicose veins due to SSV reflux were suitable for laser ablation which is now the preferred method of treatment for SSV related varicosities in our institution. In most patients the SPJ had been ligated at the

original surgery and SSV reflux was the result of communication between the truncal vein and the popliteal vein via neovascularisation. Thus it was not possible to achieve a flush SSV/SPJ ablation in most cases. Foam sclerotherapy was not employed for neovascularisation at this site since it was decided to examine its safety and efficacy in patients with SFJ neovascularisation.

Although flush ablation of the truncal/deep vein junction was not possible in most patients with SSV/GSV reflux all had a significant improvement in their symptoms scores (AVVS, VCSS). Whilst there may be some debate about the optimum site for distal cannulation of the truncal vein it is our policy to commence ablation at the lowest point of reflux when feasible. Although previous studies have reported transient sural nerve damage in 1-4% of patients following SSV EVLA (Chapter 6.1; Gibson et al., 2007), no instances of nerve injury occurred in patients with recurrent GSV or SSV varicosities in this study even when the SSV was ablated from the ankle. Careful attention to the administration of tumescent anaesthesia is likely to be the key to this.

Incompetent perforator veins may be associated with distal truncal vein reflux and recurrent varicose veins. In this series successful treatment was achieved by ablation of the truncal veins without specific intervention for the incompetent perforator. These regained competency following truncal vein ablation and this was associated with a symptomatic improvement. Although endovenous ablation of incompetent perforators has been reported by others (Proebstle et al., 2007) this was not performed in our unit during the study period.

Ablation of an incompetent truncal vein that connects distal varicosities with a proximal source of reflux (groin or popliteal fossa neovascularisation, incompetent perforating veins) appears to improve symptoms as measured by AVVS and to control the majority of visible varicosities provided cannulation is performed at or distal to the lowest point of reflux. For residual varicosities post-EVLA sclerotherapy was performed at the 6 week follow up if requested by the patient. Similar results were obtained even when the recurrent varicosities arose from pelvic veins, even though the feeding vein remained patent (but with <1s reflux). Failure to recognise

pelvic communications during the initial ultrasound assessment may result in unnecessary groin re-exploration (in surgical patients) since accurate ligation is almost impossible to achieve by this means. Clearly, varicosities arising from pelvic veins without an interim truncal vein are unlikely to be suitable for currently available endovenous laser ablation techniques.

Critics of this study might argue that the outcome of EVLA for recurrent varicose veins should have been compared with that of surgical treatment. Given the different patterns of reflux that are responsible for recurrent varicose veins and our previous experience in attempting to randomise patients between EVLA and conventional surgery for primary varicose veins (Darwood et al., 2008) it was felt that it would be impossible to recruit sufficient numbers to such a trial. Further surgical stripping of a residual GSV/SSV is not always possible during re-exploration of the groin or popliteal fossa since it may not be easily accessible. If left in-situ further recurrence is likely (Figure 6.5).

Although technical difficulty was not formally assessed, unlike the difference between recurrent and primary surgery, the techniques employed for EVLA were no different to those used when treating primary varicose veins. Further, since it was often difficult to pass the guide-wire from the truncal vein into the deep vein when treating recurrent varicose veins the safety of the deep veins was guaranteed.

Conclusions

In appropriate patients EVLA is a safe and effective treatment for recurrent varicose veins due to recurrent SFJ and SPJ reflux, perforator incompetence and pelvic vein reflux. Ablation of the responsible truncal vein improves symptoms as measured by AVVS and is associated with high levels of patient satisfaction. This was apparent at both 3 month and 1 year follow-up. Since the technique is relatively straightforward and is not associated with more complications than EVLA for primary varicose veins, the technique could be preferred to conventional surgical

treatment whenever the anatomy is suitable. Long term follow is required, particularly to assess the significance of persisting neovascularisation after EVLA.

6.4 Laser ablation for paradoxical reflux in Giacomini vein

6.4.1 Introduction

The Giacomini vein, described in 1873, is a proximal extension of the SSV in the thigh. It is present in 50-80% of the population (Moosman and Hartwell, 1964; Vasdekis et al., 1989; Labropoulos et al., 1994), and in >50% of the patients it communicates with the GSV in the thigh (Delis et al., 2004). This inter-saphenous connection may transmit reflux from the proximal GSV to the SSV (descending or orthodox reflux) or from the sapheno-popliteal junction (SPJ) to the GSV (ascending or paradoxical reflux; Georgiev et al., 2003). In paradoxical reflux, blood from the SPJ ascends through the Giacomini vein to the GSV in the thigh and feeds more distal varicosities associated with the GSV. Ante-grade flow through the Giacomini vein during both systole (compression) and diastole (relaxation) of the calf muscle is an unusual striking feature of this type of reflux which is responsible for about 1% of primary varicose veins (Georgiev et al., 2003). Although there is no consensus regarding the best treatment for this type of reflux, surgical division of the Giacomini vein flush with the SSV and the GSV has been described (Escribano et al., 2005).

This article describes a new approach to treat varicose veins due to paradoxical Giacomini vein reflux by endovenous laser ablation of the incompetent segment of GSV. The relevant fluid mechanics underlying this method of treatment are discussed.

6.4.2 Methods

Two patients aged 46 and 52 years (1 male, 1 female) presented with symptomatic primary varicose veins (aching, pruritus), without skin changes. Duplex ultrasonography (DUS) confirmed that the SFJ, proximal GSV and SSV were all competent. There was reflux at the SPJ and in the distal GSV. A Giacomini vein, which terminated at the GSV, was identified in both

patients and ante-grade flow was noted during both calf muscle squeeze and release. DUS also confirmed that the varicosities were not arising from the SSV.

Endovenous laser ablation (810 nm diode laser, 12W power, 1 second pulse with 0.1 second intervals 60-72J/cm) of the GSV was performed from the mid-calf proximally beyond the junction with the Giacomini vein. Following treatment a non-stretch compression bandage was applied for one week followed by a class 2 support stocking for a further week. Both patients were prescribed 50 mg diclofenac sodium tds for 3 days to reduce inflammatory phlebitis in the GSV and encouraged to resume their daily activities (including work) as soon as possible.

Both patients were reviewed at 6 and 12 weeks post-treatment. This included objective assessment using the AVVS scores, VCSS and DUS. Reflux status of the SPJ, GSV, SSV and Giacomini vein were all recorded.

6.4.3 Results

At six weeks, DUS confirmed that both GSVs were occluded throughout the treated length and that the SPJs had become competent. The majority of varicosities had disappeared although one patient required sclerotherapy for a residual varicosity. The improvement in symptom severity scores are shown in table 6.8. Symptoms had resolved fully in both patients. No reflux was demonstrated in the SSV in either patient, and the Giacomini vein had decreased in diameter (see table 6.9) with minimal ante-grade blood flow during calf muscle squeeze and no flow following calf release. At 12 weeks the results were similar, although the treated GSV was non-visible on DUS. No residual or recurrent varicose veins were present. The SFJ, SPJ, Giacomini vein and SSV were all competent. The duplex ultrasound scan findings in both patients are summarized in table 6.9.

	Patient 1	Patient 2
Pre AVVS	16.5	12.7
Post AVVS	2.1	0
Pre VCSS	3	3
Post VCSS	0	0
Sclerotherapy requirement	One session	None

Table 6.8: Standard outcome measurements before and 12 weeks after EVLA

AVVS: Aberdeen varicose vein score

VCSS: Venous clinical severity score

	Pre treatment	Post treatment: 3months
SFJ	Competent	Competent
Proximal GSV (proximal to Giac v)	Competent	Competent
Distal GSV (Distal to Giac v)	Reflux	Occluded/not seen
SPJ	Incompetent	Competent
SSV	Competent	Competent
Giac v	Ante-grade flow during both calf muscle squeeze and release	Ante-grade flow during calf muscle squeeze, no flow during release
Diameter of the Giac v in Patient 1	6.2 mm	3.4 mm
Diameter of the Giac v in Patient 2	5.9 mm	3.6 mm

Table 6.9: DUS findings before and after treatment

SFJ: Sapheno-femoral junction

GSV: Great saphenous vein

SPJ: Sapheno-popliteal junction

SSV: Small saphenous vein

Giac v: Giacomini vein

6.4.4 Discussion

Blood flows as a continuous column and therefore reflux in one segment of vein is filled by ante-grade or retrograde blood flow in another vein. Appreciation of this is necessary to understand the pattern of reflux and to plan effective treatment for varicose veins. In paradoxical reflux, although the blood from SPJ ascends through Giacomini vein against gravity, the blood eventually flows downwards to fill the GSV varicosities that are located below the SPJ. Even though blood appears to flow against gravity initially, the overall net-travel effect is in the direction of gravitational force. Thus, the cardinal sign of paradoxical reflux in these patients was the cephalad flow in the Giacomini vein during calf muscle release. In this type of paradoxical reflux, the SSV is competent due to a healthy valve in the proximal SSV, even though the SPJ becomes incompetent. A competent SFJ and proximal GSV are the other characteristic features of this type of reflux (Figure 6.8).

This type of paradoxical reflux can be simulated in a simple experimental model of water flow (Figure 6.9). Water ascends through the tube segment "AB" before it descends in tube segment "CD". The water flow in this model is only possible as long as the point D is lower than the point A, effectively working as a siphon. Abolition of segment CD would prevent this siphon effect and stop flow from A to C.

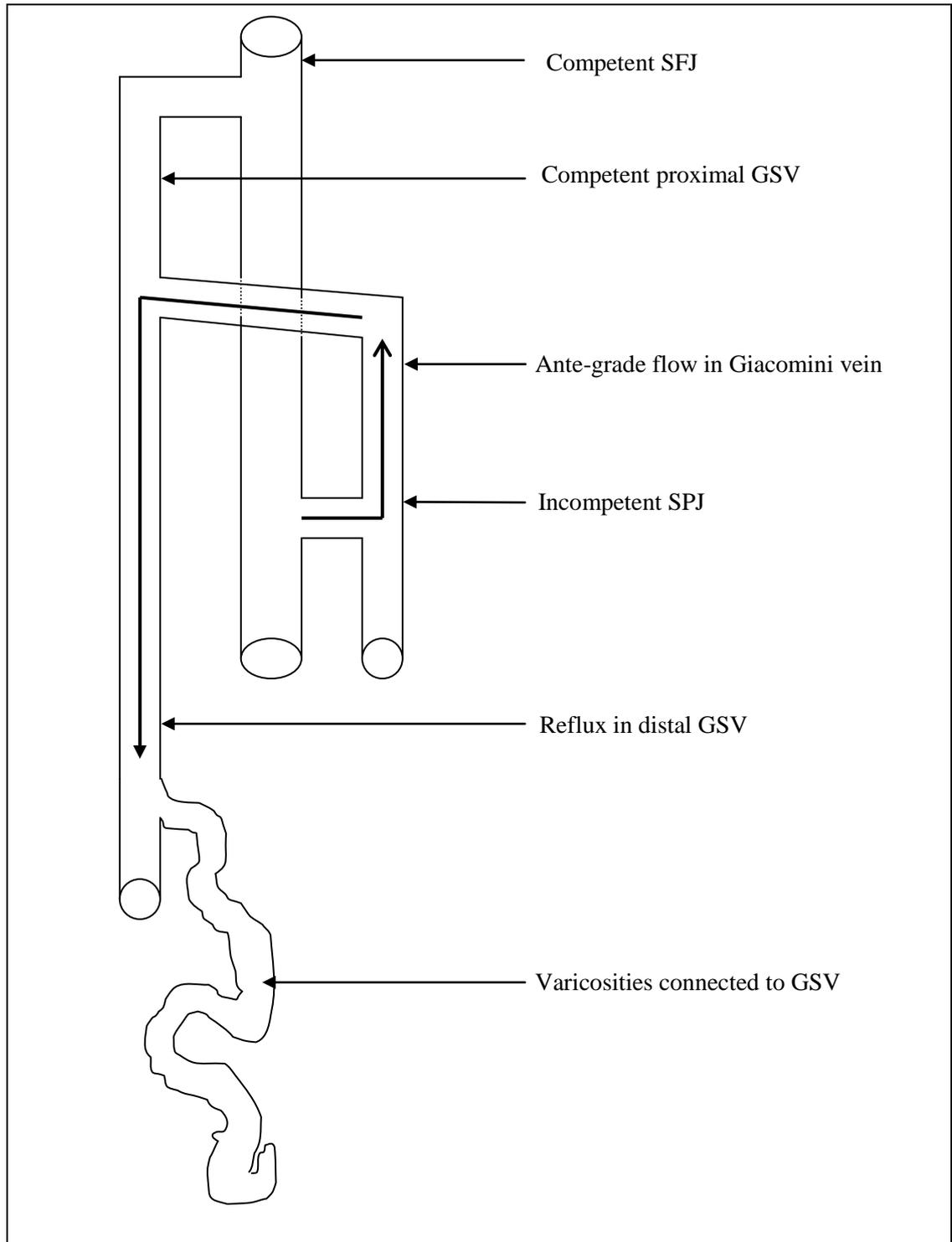


Figure 6.8: Diagrammatic representation of paradoxical reflux in a Giacomini vein

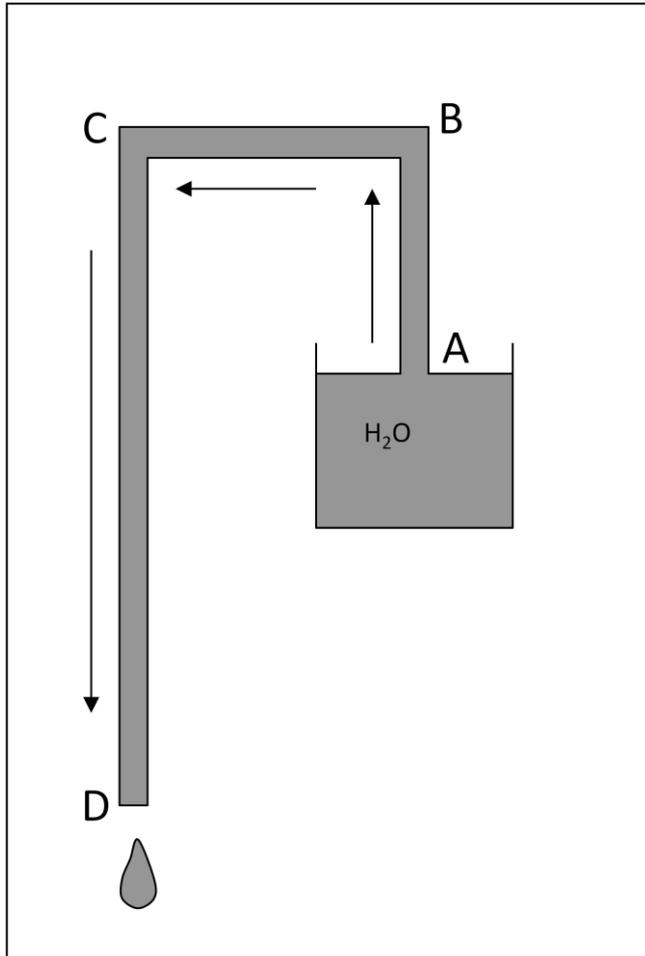


Figure 6.9: The siphon effect

(A simple model consisting of a water container and tubing demonstrates that the water column rises in segment AB before it falls with gravity in segment CD)

This provides the rationale for treating this type of paradoxical reflux by removal or ablation of the GSV. The post-treatment DUS findings confirm that such a strategy was effective since the Giacomini vein diminished in size and the SPJ regained competency. A Doppler spectral trace (DST) of paradoxical reflux in a Giacomini vein before and after GSV EVLA is shown in figure 6.10 and 6.11. Although it might be considered that the SSV might be at increased risk of becoming incompetent once paradoxical reflux in the Giacomini vein had been abolished, this did not seem to be the case as it remained competent on the 12 week follow-up DUS.

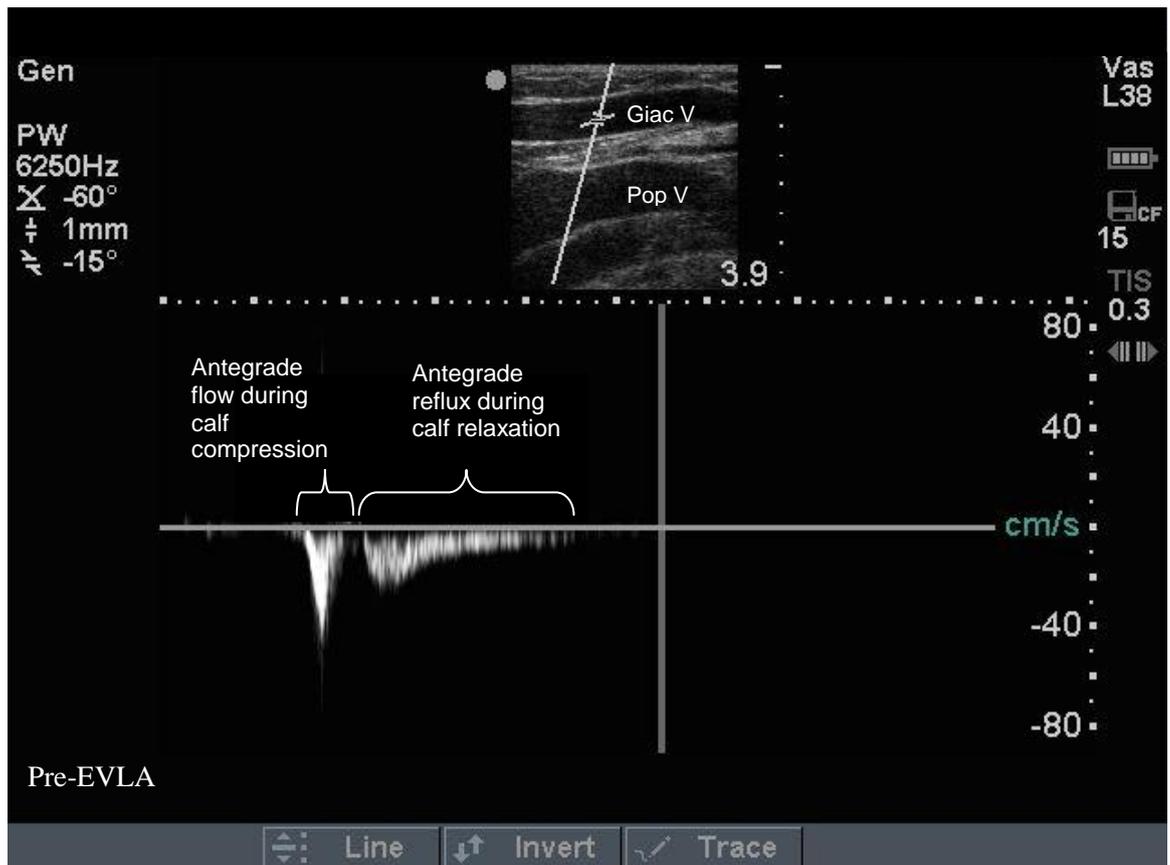


Figure 6.10: Doppler spectral trace (DST) of a Giacomini vein before GSV EVLA

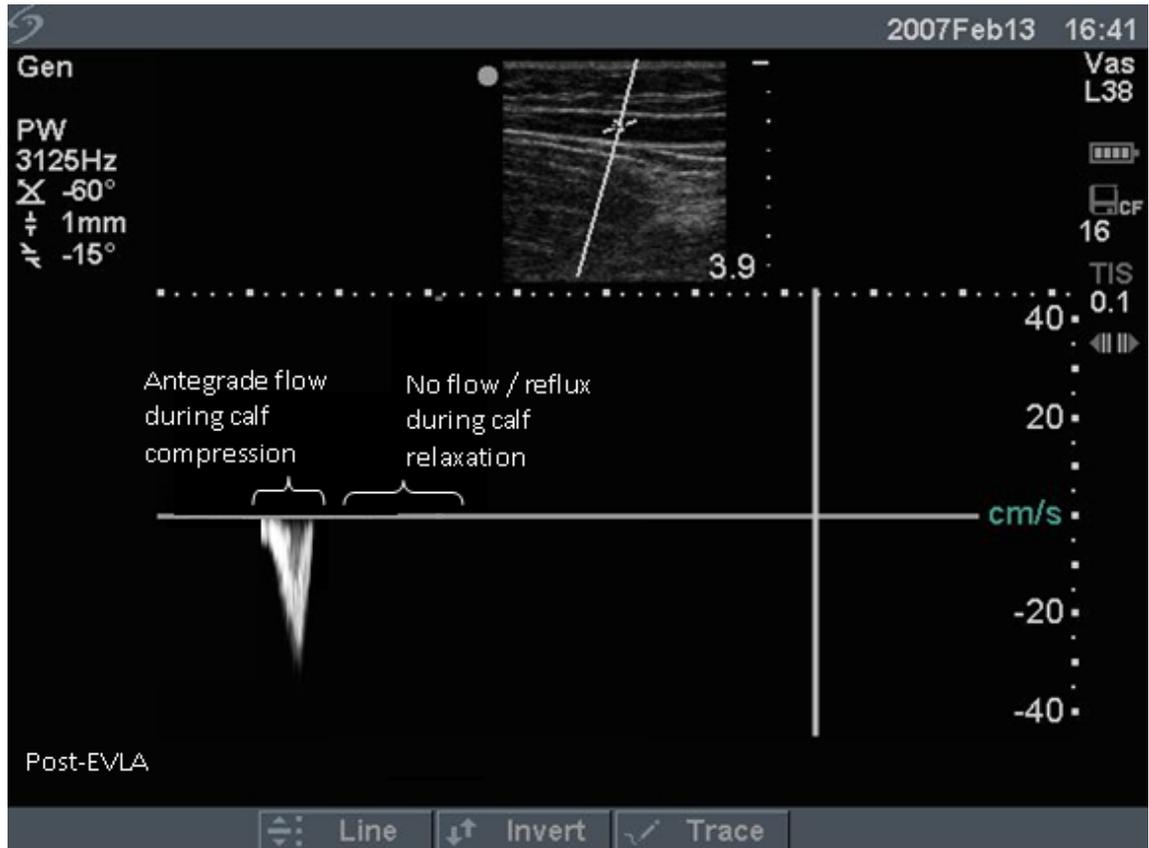


Figure 6.11: Doppler spectral trace (DST) of a Giacomini vein 12 weeks after GSV EVLA

The findings in these two patients highlight the necessity of carrying out a detailed DUS assessment to determine the pattern of reflux in each limb before planning a definitive treatment, particularly when EVLA is to be employed. Further studies with longer follow up are required to establish a standardized minimally invasive treatment for this pattern of paradoxical reflux. The main alternative to the technique described here would be ablation of the Giacomini vein. However, unless the GSV is also ablated it is likely that reflux would persist with proximal filling via GSV tributaries.

Chapter Seven:

7. Recurrence Following EVLA

7.1 Introduction

Varicose vein recurrence is common following conventional great saphenous vein (GSV) surgery, occurring in 13-29% of patients (Jones et al., 1996; Dwerryhouse et al., 1999; Turton et al., 1999) in the medium term but in 62-70% when follow-up is extended to 10-11 years (Campbell et al., 2003; Winterborn et al., 2004a). Further, some 20% of interventions for varicose veins are for recurrent varicosities following previous surgery (Dark, 1992; Ruckley, 1997). Although the causes of recurrence include incompetent perforators, para-reflux and inadequate primary surgery, groin neovascularisation is believed to be the commonest of these (Jones et al., 1996).

Currently, there is increasing interest in the use of minimally invasive treatments for varicose veins, including foam sclerotherapy and both radiofrequency and endovenous laser ablation. Critics of these techniques suggest that recurrence rates may be higher than that for conventional surgery. The aim of this current prospective cohort study was to compare the rates of recurrence and neovascularisation rates 2 years following either conventional surgery or endovenous laser ablation (EVLA) for varicose veins.

7.2 Methods

Consecutive patients undergoing treatment for primary varicose veins due to SFJ and GSV reflux between January 2004 and May 2005 were included in this study. Patients with a previous deep vein thrombosis, recurrent varicose veins, and those who also had reflux in another truncal vein (AAGSV, perforators or SSV) were excluded. All patients were suitable for either surgery or EVLA and were allowed to choose their treatment option. Of the 127 patients treated, 118 (129 limbs, 72 females, 46 males, median age 48 [32-68]) have completed 2 year follow up after either conventional surgery (Group A: 60 limbs) or EVLA (Group B: 69 limbs).

Interventions

Surgery for participants in group A was performed by a consultant vascular surgeon under general anaesthesia. A standard technique of high tie, where all tributaries at the SFJ were ligated, stripping of the GSV to the knee and multiple phlebectomies was used. Although the cribriform fascia was closed no additional surgical strategies such as a PTFE patch or over-sewing of the saphenous trunk were used to try and reduce the risk of neovascularisation.

Group B underwent standard EVLA as described previously in chapters 2 and 3 (810nm diode pulsed laser at 12W power). The GSV was ablated from the knee to the SFJ. Total laser energy (J) and energy density (J/cm) were all recorded prospectively. During follow up at 6 and 12 weeks, any residual varicosities that were palpable and >3mm in size were treated with direct injection of foam sclerotherapy if requested by the patient (ultrasound guided foam sclerotherapy to the truncal vein was not undertaken in this study).

Data collection and follow-up

Patients' pre-treatment clinical severity (CEAP) and treatment details were recorded prospectively (Patients' initial pre-treatment data was collected by my predecessor Miss Rossie Beale until Feb 2005). All patients underwent clinical and DUS using a portable ultrasound

(TITAN® Sonosite Inc, Bothell, USA) before the treatment and at 6, 12, and 52 weeks after treatment. The maximum GSV diameter was measured (DUS: avoiding focal dilatations) while standing prior to the intervention. The reflux status of the deep and all truncal veins were documented at each visit. Compressibility and detectable blood flow during calf squeeze / release in the treated vein were also recorded. A further DUS assessment was performed at 2 years when patients were also examined to determine the presence of recurrent varicose veins. Clinical recurrence was defined as the presence of palpable varicosities that measured >3mm on the treated leg that had been noticed by patient and confirmed by a clinician.

The DUS performed at 2 years again assessed the presence of reflux in the femoral vein, the SFJ or within the treated GSV. Neovascularisation (serpentine venous channels) in the groin was also identified by careful DUS assessment, with the probe held longitudinally, horizontally and at different angles. The largest diameter and the duration of reflux in these channels were documented. When present, neovascularisation was classified (Jones et al., 1996) as those of small size (<4mm) with reflux of <1s duration (Grade 1) and those with larger (\geq 4mm) veins and prolonged reflux (>1s; Grade 2). All recurrent varicosities were traced with DUS to detect the source of reflux including perforating veins in the thigh or calf. Patient satisfaction scores at 2 years were derived using a visual analogue scale as described earlier.

Statistical analysis

Recurrence and neovascularisation rates were compared between groups using a Fisher's exact test. Patients' satisfaction was compared using a Mann-Whitney U test. A p value of <0.05 was considered significant. All analyses were performed using the statistical package SPSS® for Windows (SPSS (14), Chicago, Illinois, USA).

7.3 Results

Patients' demographic details and pre-treatment disease severity are shown in table 7.1. Recurrence and neovascularisation rates are compared in table 7.2. At one year clinical recurrence was evident in 2 (group A) and 5 (group B) patients whilst DUS confirmed the presence of neovascularisation in 7 (group A) and one (group B) patients. At 2 years neovascularisation was detected in 11/60 (18%) patients following surgery and 1/69 (1%) after EVLA ($p=0.001$). Of the group A patients with neovascularisation 6/11 (55%) were classified as grade 1 and 5/11 (45%) grade 2. The single patient in group B had grade 2 neovascularisation. Overall clinically apparent, cumulative recurrence rates up to 2 years were 4/60 (6.6%) and 5/69 (7%) following surgery and EVLA respectively ($p=0.631$).

In group A, 2 patients developed recurrence due to an incompetent thigh perforator by 1 year and 2 were due to neovascularisation promoting reflux in a persisting incompetent GSV (inadequate/inaccurate stripping) at 2 years. A further 9 patients showed evidence of groin neovascularisation on DUS but without clinical recurrence at 2 years.

All recurrences in group B were evident by one year and 3/5 (60%) occurred following early GSV re-canalisation by 12 weeks. These patients all received $<50\text{J/cm}$ laser energy during EVLA. Of these 3, one patient also had grade 2 neovascularisation associated with GSV re-canalisation. The remaining 2/5 (40%) recurrences were due to an incompetent mid-thigh perforator ($n=1$), and reflux into the anterior accessory great saphenous vein (AAGSV, $n=1$). At 2 years, patients' satisfaction rates were 90% and 88% in groups A and B respectively ($p=0.37$).

Patients	Group A (n=60) (Surgery group)	Group B (n=67) (EVLA group)	p
Age (median \pm iqr)	46 (32-60)	49 (30-78)	0.43
Male: Female	39:21	45:22	0.49
Previous DVT	0	0	-
Number of limbs	64	73	
<i>Pre-treatment C of CEAP*</i>			
C2	39	43	0.42
C3	12	13	
C4	12	14	
C5/6	1	3	
GSV diameter (mm, median \pm iqr)	7.8 (iqr 5.8-9.1)	8.1 (iqr 5.9-9.3)	0.24

Table 7.1: Baseline characteristics of patients in Group A (surgery) and Group B (EVLA)

* Pre treatment C of CEAP classification (EAP of CEAP were the same in all patients, see exclusion criteria)

1 year (n=limbs)	Group A (n=63)	Group B (n=71)	p
Clinical recurrence	2/63 (3%)	5/71 (7%)	
Incompetent perforator	2 (3%)	1 (1%)	
Re-canalisation / residual GSV	0 -	3 (4%)	
Reflux into the AAGSV	0 -	1 (1%)	
Neovascularisation	7/63 (11%)	1/71 (1%)	
2 years (n=limbs)	Group A (n=60)	Group B (n=69)	p
Clinical recurrence	4/60 (7%)	5/69 (7%)	0.44
Incompetent perforator	2 (3%)	1 (1%)	0.45
Re-canalisation / residual GSV	2 (3%)	3 (4%)	0.36
Reflux into the AAGSV	0 -	1 (1%)	0.53
Neovascularisation	11/60 (18%)	1/69 (1%)	0.001

Table 7.2: Comparison of recurrence patterns and neovascularisation rates between groups A and B

AAGSV: Anterior accessory great saphenous vein

Two patients in group B had an active leg ulcer and a further patient in this group and one patient in group A had healed ulcers prior to the treatment. Following treatment, the active ulcers healed by 12 weeks in one patient and by 6 months in the other. All healed ulcers remained healed at 2-year follow up.

7.4 Discussion

Overall recurrence rates were similar for both conventional surgery and EVLA 2 years after treatment. However, DUS detectable groin neovascularisation was significantly more common after surgery. In contrast, most recurrences following EVLA reflected inadequate primary treatment and it is likely that these could have been prevented by the administration of $\geq 70\text{J}/\text{cm}$ laser energy to the vein (Chapter 3). The different patterns of recurrence following EVLA and surgery are summarised figure 7.1 and 7.2.

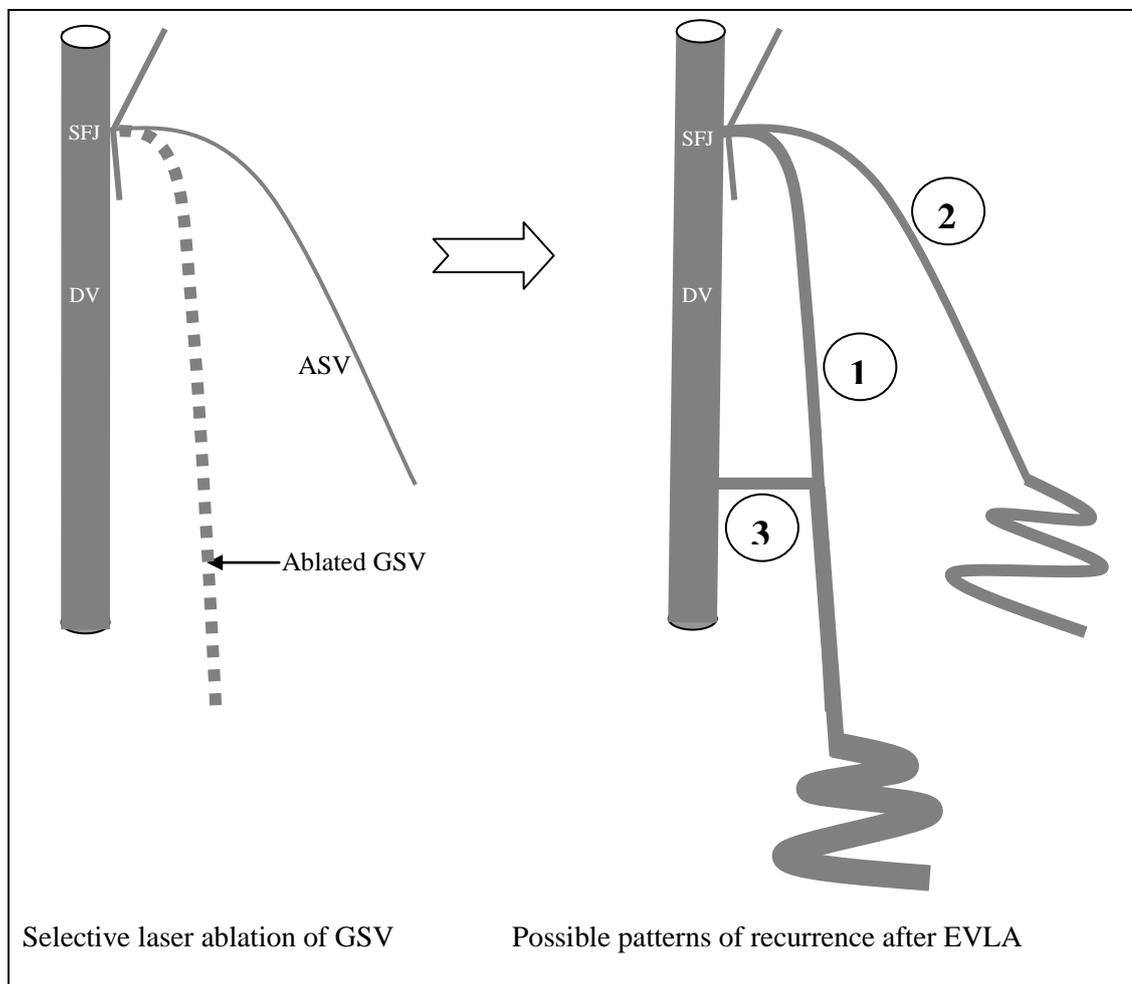


Figure 7.1: Possible patterns of reflux after EVLA

1: Re-canalisation, 2: Para-reflux (AAGSV), 3: Perforator incompetence

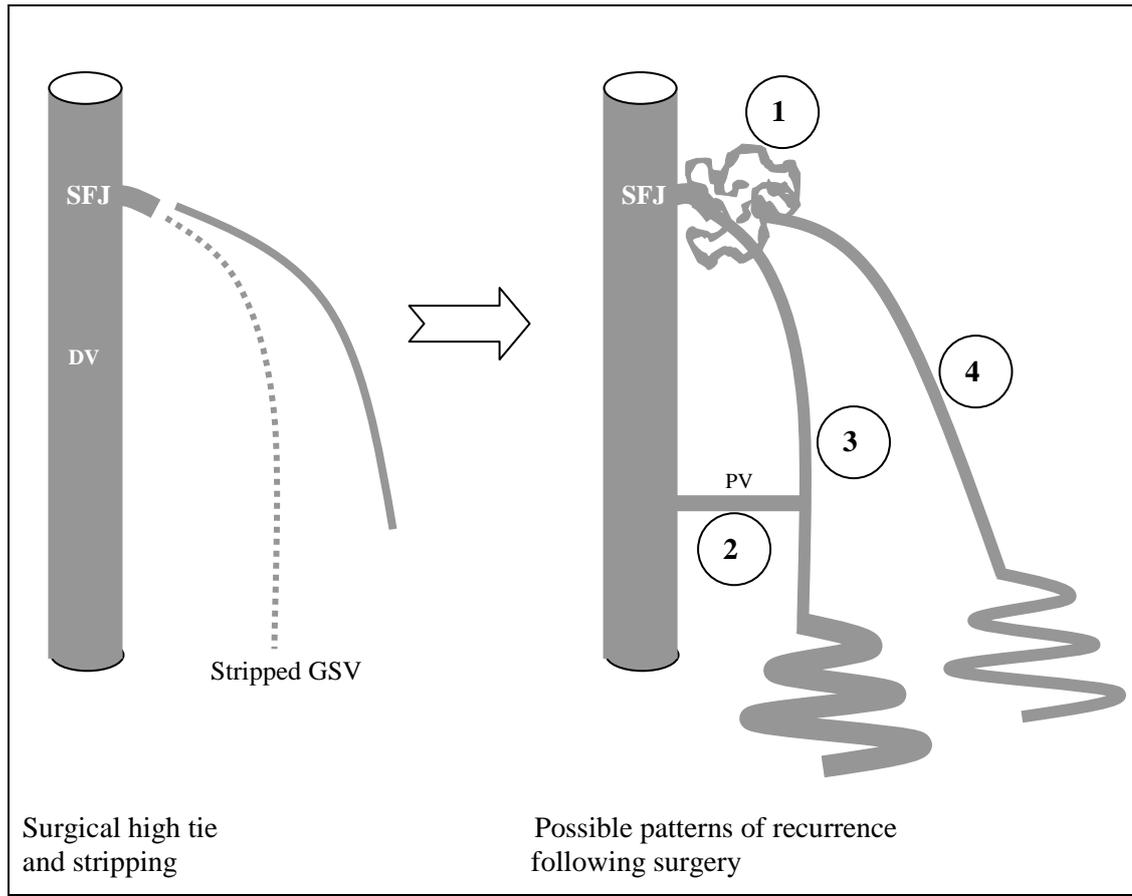


Figure 7.2: Possible patterns of reflux after surgery

- 1: Neovascularisation
- 2: Incompetent perforating vein
- 3: Persisting GSV/ new vessel formation
- 4: Para-reflux (AAGSV) connecting via neovascularisation

Varying frequencies (8-60%) (Jones et al., 1996; Nyamekye et al., 1998; van Rij et al., 2004; De Maeseneer et al., 2005; Egan et al., 2006; Perrin et al., 2006) of neovascularisation have been reported after surgery which probably reflects the duration of follow-up, possibly differences in surgical technique, and the sensitivity of DUS and the operator. Neovascularisation was detected in 18% (11/60) of this series with 5/11 (45%) having grade 2 neovascularisation which is more likely to be associated with a higher risk of recurrence. Although clinically obvious

recurrence was not documented in most patients, Maeseneer et al. in 2005 have shown that neovascularisation rates at 1 year predict the development of clinical recurrence at 5 years.

Histological studies have suggested that neovascularisation is the result of angiogenesis following surgery (Nyamekye et al., 1998). Techniques that have tried to reduce this risk have produced varying results. Over-sewing the stump (Winterborn and Earnshaw, 2007) or covering it with a pectineus flap (Gibbs et al., 1999) have not proved successful although the use of a silicon patch to separate the SFJ from the GSV tract may be of benefit after surgery for recurrent varicose veins (de Maeseneer et al., 2004a). However the latter has been associated with femoral vein stenosis (de Maeseneer, 2004b) and the same author (de Maeseneer et al., 2007) now recommends closure of the cribriform fascia although this technique has not been subject to vigorous assessment in a randomised clinical trial. Finally although de Maeseneer found that a silicone patch reduced the risk of further recurrence Earnshaw's group reported no benefit following implantation of a PTFE patch.

As EVLA ablates the target vein from within the outer vein wall should remain largely intact and thus exposure of endothelial cells to the healing peri-venous tissue and subsequent neovascularisation should be less frequent. Nevertheless one patient in this series did develop neovascularisation following EVLA and vein wall perforation and haematoma formation are a likely explanation for this. This reduction in neovascularisation has also been reported following radiofrequency ablation (Kianifard et al., 2006) and although there are no studies examining its frequency following DUS guided foam sclerotherapy it seems likely that the results would be similar to those for the other endovenous techniques.

Residual varicosities that persist after EVLA should be differentiated from recurrent varicose veins that subsequently appear. The presence and extent of residual varicosities depend on their pre-EVLA anatomical distribution and the haemodynamic relationship with the incompetent truncal vein. Varicosities that are directly connected to the incompetent truncal vein tend to

shrink when the index truncal vein is ablated both below and above their origin. However varicosities that have an additional cross communication with another vein tend to remain as residual varicosities. A previous study has shown that laser ablation of the GSV from below the lowest point of reflux, and therefore distal to the lowermost varicosity reduces the requirement of foam sclerotherapy to 17% (Chapter 5).

Following ablation of a single incompetent truncal vein, neo-reflux into another truncal vein, is theoretically possible. This occurred in one patient in this study who developed AAGSV reflux following GSV ablation. This could either represent new reflux or the failure of pre-treatment DUS to identify concomitant AAGSV incompetence. The latter may be more likely since previous studies have shown that SFJ tributaries remain competent following selective EVLA of refluxing truncal veins (chapters 4.2 and 6.2).

Re-canalisation may occur in up to 4% of limbs following EVLA, although most are not associated with recurrent varicose veins unless it occurs within 6 weeks of treatment (primary treatment failure) (Proebstle et al., 2004). When re-canalisation occurs early it is almost always associated with the delivery of low energy densities ($<60\text{J/cm}$). Given the current recommendation to employ $\geq 70\text{J/cm}$, it is anticipated that of this type of recurrence would be uncommon in the future.

A residual GSV was responsible for recurrence in 2 patients in group A. This could reflect either incomplete stripping or the presence of a duplex GSV. Whilst both veins can be easily stripped when the GSV is duplicated from the groin, this becomes more difficult when a duplex GSV arises some distance from the surgical incision. This highlights the potential benefit of ultrasound control both pre- and intra-operatively in patients undergoing conventional surgery. In contrast, EVLA is performed under ultrasound control and thus both veins can be easily ablated regardless of the anatomical site of the duplex system.

Incomplete groin dissection, usually by trainee surgeons, has also been implicated in the pathogenesis of recurrent varicose veins (Negus, 1993; Redwood and Lambert, 1994). Certainly, in this study this should not have been a factor since all surgery was performed by a consultant vascular surgeon. Further, with increasing sub-specialisation within general surgery and the imminent separate specialty status for vascular surgery future recurrences resulting from inadequate surgery should be less likely. Moreover incomplete stripping of the incompetent truncal veins due to varying GSV anatomy, unidentified perforator incompetence or groin neovascularisation are likely to assume increasing importance. Thus the outcome of surgery might be improved by ensuring complete GSV stripping by employing DUS guidance, particularly when a duplex GSV is present.

Incompetent perforating veins were the cause of recurrence following both surgery and EVLA and have been reported as the principle factor in up to 14% of patients with recurrent varicose veins following surgery (Redwood and Lambert, 1994). Such a pattern of reflux may occur following neovascularisation within strip-tract haematoma or after incomplete stripping of the incompetent truncal vein. It is therefore important that pre-treatment imaging identifies any perforators and that stripping or laser ablation is performed from the groin to a point distal to the perforating vein. In this respect, a potential advantage of EVLA is the ability to ablate an incompetent GSV beyond possible sites of perforating veins such as Boyd's perforators in the proximal calf without a significant risk of saphenous nerve injury which may occur following surgical stripping. Although some authors claim that untreated incompetent perforator vein become competent following surgical stripping due to changes in the venous haemodynamics (Blomgren et al., 2005), others claim that even after ligation of an incompetent perforator up to 75% of limbs will develop new perforator reflux at 3 years (van Rij et al., 2005). Similar studies after thermal ablation are not available at present. Thus it is not clear if recurrences due to incompetent perforators following EVLA occurs from perforators that were incompetent prior to treatment or if this has developed de novo. Whilst the former could be a satisfactory

explanation following above-knee EVLA and subsequent below-knee perforator reflux the latter may be more relevant in patients who re-present with and incompetent perforator in the thigh.

In conclusion, different patterns of recurrence occur after EVLA and surgery. Although the overall recurrence rates for both techniques were similar at 2 year follow-up re-canalisation after laser ablation should be minimised by modifying laser energy delivery. In contrast neovascularisation is likely to remain a significant problem following conventional surgery although more widespread use of careful ultrasound assessment might ensure more complete stripping of the GSV and any associated incompetent truncal veins. Nevertheless the very low incidence of neovascularisation following EVLA suggests that recurrence rates might be lower with this technique after successful ablation of incompetent truncal veins.

Chapter 8:

8. Summary and Concluding Comments

Most studies in my thesis apart from that presented in chapter 5 consist of non-randomised consecutive sampling. Further, small sample size, lack of randomisation or prospective controls and lack of long term follow-up are considerable weakness of most studies in this thesis. However, there are now many studies confirming the safety and efficacy of EVLA in the treatment of varicose veins. Further, studies included in this thesis have shown that the technique can be applied to a range of patients with superficial venous incompetence rather than simply those with GSV reflux as initially conceived.

EVLA is a minimally invasive thermal ablation technique that is effective in treating varicose veins of the lower limb. It abolishes reflux at the deep to superficial vein junction by ablating the incompetent superficial truncal vein. It can be used for the treatment of both primary and recurrent varicose veins arising from the sapheno-femoral and sapheno-popliteal junctions including the anterior accessory great saphenous vein. In addition it can also be used to ablate incompetent perforator veins and treat patients with paradoxical reflux. The procedure improves symptoms and disease specific quality of life with outcomes that are at least as good as surgery when the techniques have been compared in randomised trials. Work in this thesis has also shown that the maximum improvement in disease specific quality of life is achieved by ablation of the truncal vein to the lowest point of reflux and that this can be safely achieved without concomitant nerve injury, the latter being an important complication of below-knee GSV stripping.

As with any new technique long term outcome data is still required to confirm the durability of the procedure. However it is now clearly recognised that EVLA results in irreversible damage to the ablated vein and that truncal vein occlusion is the result of progressive fibrosis and

obliteration of the vein rather than thrombotic occlusion. Thus the treated vein becomes invisible within 6-12 months provided that sufficient energy has been delivered to the vein. In patients where recanalisation does occur this is usually evident within 6 (technical failure) to 12 weeks (inadequate energy delivery resulting in thrombosis rather than fibrotic occlusion). Thereafter recanalisation is uncommon, and if it occurs the truncal vein is small with only flash or no reflux.

In respect of the future risk of recurrent varicose veins concerns about the role of the tributaries of the SFJ that are not always disconnected from the junction by EVLA but are ligated during surgery appear unfounded as shown earlier in this thesis. Similarly the development of neo-vascularisation at the SFJ is markedly less common than that after surgical ligation in patients followed up 2 years after both treatments. These findings would again imply that the risk of developing recurrent varicosities may be lower for EVLA than surgery. Again longer follow-up is needed.

A further and unexpected advantage of the newer minimally invasive techniques for the treatment of varicose veins has been the widespread use, after appropriate training, of duplex ultrasound by surgeons. This has led to a greater understanding of the pathophysiology of venous disease and improved decision making in terms of selecting the most appropriate treatment modality for patients. It has also improved patient care with many clinics now performing ultrasound assessment at the patient's first visit and making a definitive treatment recommendation at that time. This thesis also describes a new method of determining reflux severity in a truncal vein based on the ultrasound findings which has the potential to further aid accurate decision making in patients presenting with varicose veins.

8.1 Future advances in the endovenous management of superficial venous incompetence

Although 80% or more of new patients presenting with varicose veins are suitable for EVLA the remainder are not. Generally these patients either have no significant truncal vein that is present for treatment (e.g. varicosities arising directly from the SFJ after previous surgery, an AAGSV that is varicose from the SFJ) or the incompetent truncal vein is considered too tortuous to allow passage of a guidewire and sheath. For the former it is difficult to imagine that future technical advances will provide a method for achieving endovenous ablation other than by ultrasound guided sclerotherapy. For the second group there are various techniques that might improve the rate of successful cannulation. These include the use of hydrophilic guidewires and using DUS to help steer the guidewire away from tributaries. It should also be possible to enhance cannulation rates by using sheaths of differing shape/angle at the tip to steer the guidewire through the vein.

8.1.1 Modification on laser physics

Earlier in this thesis the potential benefits of longer wavelength lasers has been considered. Preliminary evidence would suggest that these target laser energy at the vein wall, particularly in combination with a radial fibre and that successful ablation can be achieved with less energy. This appears to be associated with a marked reduction in post-treatment discomfort. Further, it was initially proposed that with these reduced energy levels tumescent anaesthesia might not be required although this has not proved the case.

8.1.2 Predicting residual varicosities

An important and widely debated dilemma associated with the use of EVLA has been whether the varicosities should be treated concomitantly with the laser therapy or after a delay to allow spontaneous resolution following correction of the venous hypertension. The arguments surrounding this issue have been considered earlier in the thesis. Similarly the choice of either sclerotherapy or phlebectomy for residual veins has also been considered. The ability to predict which varicosities are likely to remain after successful endovenous therapy would allow suitably tailored treatment to be undertaken at the time of EVLA and further clinical studies examining this possibility are required.

8.2 Is surgery obsolete?

The increasingly widespread use of minimally invasive endovenous therapies for varicose veins has markedly reduced the requirement for conventional surgery. This has important implications in respect of both the direct and indirect costs of treatment. For the latter there is a negligible requirement for community nursing services and generally a more rapid return to normal activities including work. Within secondary care cost savings are associated with the need for fewer staff and the use of a treatment room rather than an operating theatre for the procedure. These are all powerful incentives favoring the adoption of minimally invasive therapy.

However, it has already been considered that up to 20% of patients are not suitable for EVLA for anatomical reasons. For these surgery is often considered the most appropriate alternative. Nevertheless the majority of these patients are likely to be suitable for ultrasound guided foam sclerotherapy. Whilst this technique is easy to employ the main drawback is the relatively high risk of recanalisation of the treated vein and the reappearance of the varicosities. Despite the comparatively low cost of treatment some surgeons consider it counterintuitive to offer a therapy that may be less successful in the medium or long term despite potential savings. This would not be the case if the efficacy of sclerotherapy could be enhanced.

Current research in this field is directed at developing a clearer understanding of the mechanisms by which sclerotherapy works and in enhancing the damage that is inflicted on the vein wall so that permanent ablation is achieved. If this proves successful the surgery may become obsolete!

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10. Appendix

A1: RCT Protocol

Protocol for Randomized Controlled Trial of standard EVLA versus standard EVLA with below-knee foam sclerotherapy versus above and below-knee EVLA for varicose veins.

(Endovenous laser ablation: EVLA)

Background

Varicose veins are common, affecting up to 20 % of the population. Patients seek treatment for aching legs, poor cosmesis, or complications (eczema, phlebitis, lipodermatosclerosis or ulceration). Their treatment incurs significant cost to both the NHS and employers. The majority (at least 70%¹) are the result of sapheno-femoral (SF) and long saphenous vein (LSV) incompetence and standard treatment (SF ligation, LSV stripping, multiple avulsions), requires day unit or overnight admission (particularly for bilateral varicose veins) and a general anaesthetic.

Minimally invasive techniques have been developed as alternatives to surgery, in an attempt to reduce the morbidity from surgery and to reduce recovery time. Recently Endovenous Laser Ablation (EVLA) has been developed as a minimally invasive method for treatment of varicose veins. This technique is effective and safe and is used routinely for treating patients within the Leeds teaching Hospitals NHS Trust. However modification to this technique might improve clinical outcome.

Following abolition of reflux in the above knee LSV by EVLA the distal varicose varicosities diminish in size or become non-visible. For those that are still apparent delayed foam sclerotherapy is performed approximately 6 weeks after LSV ablation. In our experience about 50% of patients require sclerotherapy and some may need up to three sessions.

Potential changes to the EVLA technique, which might reduce the requirement for sclerotherapy for below-knee varicosities includes:

- 1) Laser ablation of the below-knee LSV
- 2) Foam sclerotherapy of the below-knee LSV at the same time as EVLA (laser ablation of the above-knee LSV)

Proposed Study

This study will compare the safety and efficacy of EVLA in a randomised study of three groups of patients

- 1) Standard above-knee EVLA and delayed sclerotherapy if required
- 2) Standard above-knee EVLA with synchronous foam sclerotherapy to below-knee LSV and delayed sclerotherapy if required
- 3) Above and below knee EVLA and delayed sclerotherapy if required

A potential complication of below-knee laser ablation might be an increased incidence of saphenous nerve injury. Such injury occurs following heat transfer from LSV to the adjacent saphenous nerve or one of its branches. However the nerve remains intact and our experience with above-knee laser therapy indicates that the nerve always recovers spontaneously. This is in contrast to surgery when persistent numbness may occur (up to 10% of patients) due to irreversible damage to the saphenous nerve.

The endpoints of this study will be:

- Technical success of EVLA (duplex ultrasound assessment)
- Number of follow up sclerotherapy sessions required
- Improvement in symptoms (Aberdeen Vein Score)
- Improvement in overall quality of life (SF-36 and EuroQol)
- Post-operative mobility (medical outcomes study physical functioning measure)
- Post-operative pain – daily visual analogue score for pain and analgesia diary
- Assessment of saphenous nerve function (mapping and follow-up of any cutaneous numbness)
- Time to return to work
- Patient satisfaction
- Improvement in cosmesis - patient and independent assessor (quantitative assessment of pre and post procedure photographs)
- Rate of complications – nerve injury, haematoma, phlebitis, infection, deep vein thrombosis (duplex documentation)

Patients

Inclusion criteria:

Consecutive consenting patients presenting to the vascular clinic for treatment of below- knee varicose veins (with or without thigh varicosities) that are due to LSV reflux.

Exclusion Criteria:

- Failure to obtain consent
- Patients under 18 years of age
- Patients having no below-knee varicose veins
- Known allergy to sclerosing agent

Randomisation: Block randomisation will be performed into the three groups described above.

Randomising method: Sealed envelope, opened when the patient has consented to take part in the trial.

Blinding: Unfortunately it will not be possible to blind the patient or the operator to the type of procedure. However the independent assessor, who can be blinded, will assess the pre and post procedure photographs.

Treatment Schedules

Treatment will be carried out at one of three centres: Leeds General Infirmary, St James University Hospital or BUPA Hospital at Leeds. All patients will be under the care of the consultant vascular surgeons at the General Infirmary at Leeds.

Group 1- Standard EVLA alone

This uses an 810nm bare-tipped, pulsed laser (Diomed Inc) at a power of 12 watts. The standard technique for EVLA will be used employing a laser density of 5 pulse/cm. Delayed foam sclerotherapy up to 5 ml of 0.2-1% STD will be used as required at the follow up clinic visit/s.

Group 2- Standard EVLA and on table foam sclerotherapy

The same EVLA technique as for group 1 will be used except that the LSV will be cannulated below-knee (mid-calf) and a 70 cm sheath inserted. The LSV will be ablated (EVLA) to the level of the knee joint following which 5ml 1% STD (2 ml 1% STD, 3 ml air) will be injected into the below knee LSV via the sheath as it is withdrawn. Delayed foam sclerotherapy up to 5 ml of 0.2-1% STD will also be used as required at the follow up clinic visit/s.

Group 3- Above and below-knee EVLA

The LSV will be cannulated below-knee (mid-calf) and the whole length of the LSV ablated using the standard EVLA technique. Delayed foam sclerotherapy up to 5 ml of 0.2-1% STD will also be used as required at the follow up clinic visit/s.

Pre-treatment Assessment

- Basic demographic data - age, sex, occupation, anti-platelet medication
- Ultrasound duplex assessment - site of reflux, size of the long saphenous vein
- Symptom Assessment (quality of life measure) - Aberdeen Vein Questionnaire (disease-specific)
- Severity of Venous Disease - VCSS Score and CEAP score

Post treatment assessment

At 1 week: Daily Visual Analogue Score for pain
 Analgesia diary
 Time to normal activity – time to return to work
 Assessment of post-treatment complications

Duplex assessment of LSV and deep veins for evidence of DVT

At 6 weeks: Outstanding data from week 1
 Late complications
 Time of return to work if >1 week
 Injection sclerotherapy as required in all patients
 Duplex assessment of LSV

B) Secondary Outcome Measures

- Post-procedure pain - patient analgesia diary
 - daily Visual Analogue Score for pain during the first week
- Cosmesis
 - as scored by the patient and an independent assessor on a visual analogue score (VAS)
- Complication rates - wound infection, haematoma, nerve injury, DVT
- Patient satisfaction
 - would they have the same treatment again if required?
- Overall Quality of Life
 - SF-36 questionnaire

Analysis of data

1) Comparing improvement in Aberdeen Vein Score in between groups:

This is to compare the improvement in symptoms across groups, to see whether one treatment is better than another for improving symptoms. Analysis would therefore be performed using a two-group crossover t-test for equivalence.

2) Post procedure outcome:

Technical success, the number of sclerotherapy sessions, cosmeses, post treatment complications (phlebitis, saphenous nerve injury, DVT) will be compared in the three groups. The power calculation will be based on sharing equivalence.

3) Power Calculations

Comparing the requirement of follow-up sclerotherapy sessions

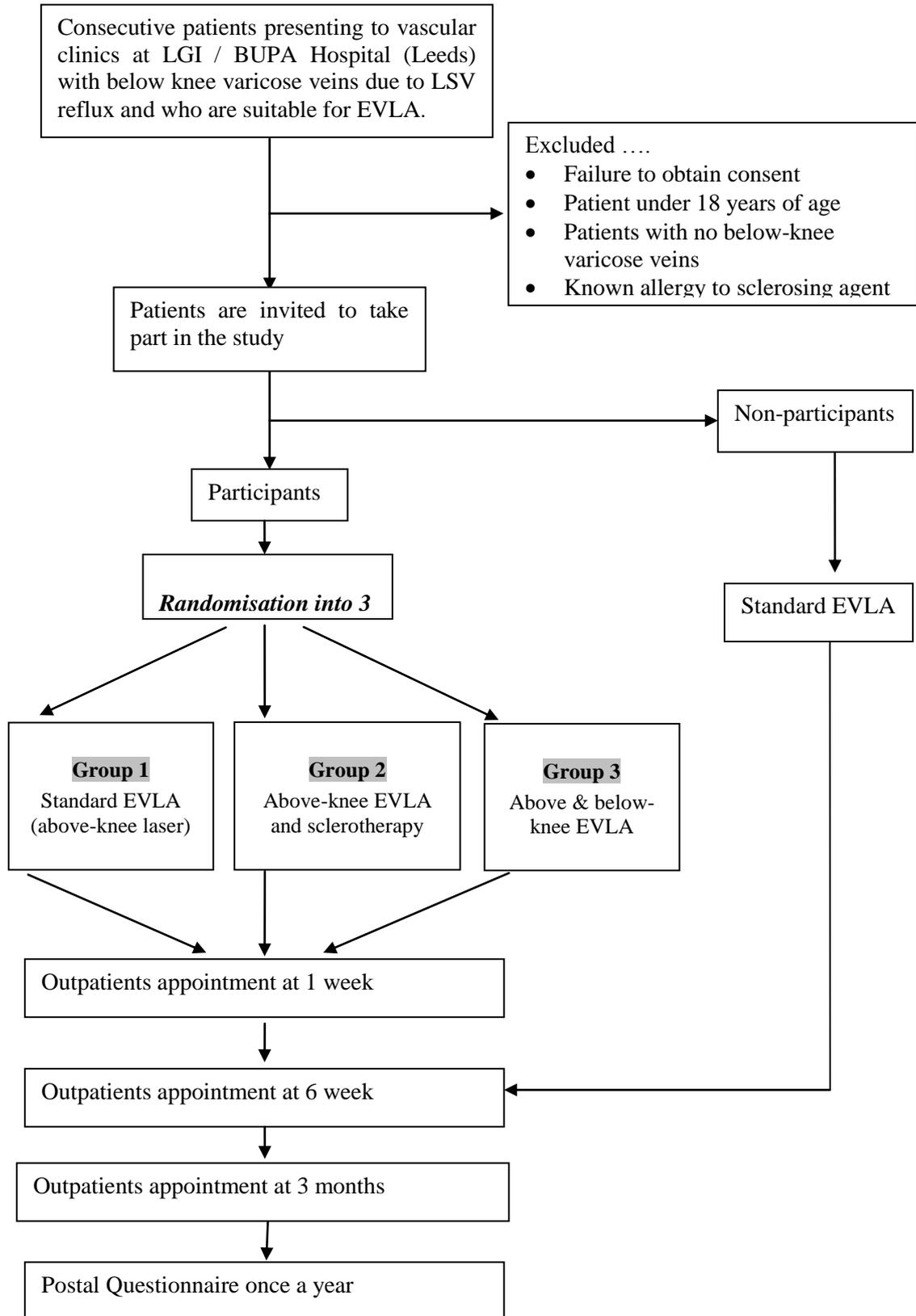
This is to compare the follow-up sclerotherapy requirement across groups, to see if one modified treatment technique is significantly better than the other technique. From our pilot study we found that the standard EVLA require follow-up sclerotherapy in 48% and the mean of the required sclerotherapy sessions was 0.66 with standard deviation of 0.812. For this study we are expecting that the sclerotherapy requirement would be half with the modified technique. Analysis will be performed using two sample t-tests of equal proportions. Power calculations are for 80% power at the 5% level of significance

This results in number per group of 32.

4) Recruitment/time scale of randomised trial

Currently approximately 450 interventions for varicose veins are performed each year. Recruitment is planned over 24 months during which time an estimated 450 patients (50% of 550) should be suitable for this study. The study group sizes allow for a 36% failure to obtain informed consent. Total patients required from power calculations = 288

Flow chart 1- Below-knee VV Trial



References

1. Gotten G., Yellin A. Ambulatory Stab Avulsion Phlebectomy for Truncal Varicose Veins. *Am J Surg* 1991, 162:166-174
2. Min RJ et al. Endovenous laser treatment of the incompetent greater saphenous vein. *J Vasc Intervent Radiol* 2001, 12:1167-71
3. Personal communication from RJ Min
4. Proebstle TM, Lehr HA, Kargl A et al. Endovenous treatment of the greater saphenous vein with a 940nm-diode laser: Thrombotic occlusion after endoluminal thermal damage by laser-generated steam bubbles. *J Vasc Surg* 2002;35:729-736.
5. Lees T, Singh S, Beard J. et al Prospective Audit of Surgery for varicose veins. *British Journal of Surgery* 1997;84: 44-46
6. Dwerryhouse S, Davies B, Harradine K et al Stripping the long saphenous vein reduces the rate of re-operation for recurrent varicose veins: Five-year results of a randomised trial *Journal of Vascular Surgery* 1999;29:589-92
7. Sarin S, Scurr JH and Coleridge Smith PD. Assessment of stripping the long saphenous vein in the treatment of primary varicose veins. *BJS* 1992;79:889-893.
8. Mackenzie RK, Lee AJ, Paisley A et al. Patient, operative and surgeon factors that influence the effect of superficial venous surgery on disease-specific quality of life. *J Vasc Surg* 2002;36:896-902
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A2: Consent form

Patient identification number for this study:.....

Consent Form for Research Study

EVLA TECHNIQUE TRIAL - Is modified Laser technique the Best Way of Treating below-knee Varicose Veins?

Researcher: Mr Nada S Theivacumar

- I have read the information sheet for the above study
- I have had the opportunity to ask questions about the study, and to discuss it with family and friends.
- I understand the purpose of the study and how I will be involved
- I understand, and accept, that as is explained in the information sheet the treatment I will receive may possibly have some side effects.
- I give permission for responsible individuals from regulatory authorities to have access to my medical notes where it is relevant to my taking part in the research. This is on the understanding that no personal details which might identify me will be presented or published without my permission.
- I confirm that I will be taking part in this study of my own free will, and I understand that I may withdraw from it, at any time and for any reason, without my medical care or my legal rights being affected.

I agree to take part in the above study.

Patient Signature: _____

Patient Name: _____

Date: _____

I have explained the trial to the patient and given them the opportunity to ask questions.

Doctor Name: _____

Doctor Signature: _____

Date: _____

A3: Patient Registration Sheet

Please complete at ultrasound clinic visit for all patients eligible for entry to trial.

Date				
Hospital Number				
Surname				
Forename				
Date of Birth				
Sex	Male <input type="checkbox"/>			Female <input type="checkbox"/>
Side to be treated	Right <input type="checkbox"/>			Left <input type="checkbox"/>
Telephone number (and time can contact)				
Ultrasound Assessment				
Diameter LSV (while standing) in mm	2cm distal to SFJ <input type="checkbox"/>			Medial to knee <input type="checkbox"/>
Echogenicity LSV	Below-knee <input type="checkbox"/>			
Compressibility LSV	Iso <input type="checkbox"/>	Hyper <input type="checkbox"/>	Hypo <input type="checkbox"/>	
Flow LSV above-knee	Not <input type="checkbox"/>	Partially <input type="checkbox"/>	Completely <input type="checkbox"/>	
Flow LSV below-knee	No flow <input type="checkbox"/>	<1sec reflux <input type="checkbox"/>	>1sec reflux <input type="checkbox"/>	
SFJ competence	No flow <input type="checkbox"/>	<1sec reflux <input type="checkbox"/>	>1sec reflux <input type="checkbox"/>	
	Competent <input type="checkbox"/>			Incompetent <input type="checkbox"/>

GP Details	
-------------------	--

To be completed on consent and randomisation:

Consent to enter trial	Yes <input type="checkbox"/>	No <input type="checkbox"/>	
Treatment Allocation	EVLT 1 <input type="checkbox"/> Standard EVLT	EVLT 2 <input type="checkbox"/> A/K&B/K EVLT	EVLT 3 <input type="checkbox"/> EVLT &Foam

A4: Baseline Data

To be collected when patient attends for treatment.

Name Hospital Number Date of Birth (or ID label)	
Patient Occupation	
Family History (1 st degree relative)	Yes <input type="checkbox"/> No <input type="checkbox"/>
Anti-platelet medication?	
VCSS score	_____ /30
CEAP Score	C_____ E_____ A_____ P_____
Check – SF-36 - EuroQol - Aberdeen Vein Score - Photo	

Please turn over....

A5: Treatment Data

Date	
Hospital Number	
Treatment Group	Standard EVLT (1) <input type="checkbox"/> Full length EVLT (2) <input type="checkbox"/> EVLT & Foam (3) <input type="checkbox"/>
Start Time (apply prep)	
Total Laser Dose (EVLТ)	
Total Length Vein Treated (EVLТ)	_____ <u>cm</u>
Rate of Pullback (EVLТ)	_____ <u>Pulse/cm</u>
Length of vein foamed	_____ <u>cm</u>
Volume of Sclerosant / air	Sclerosant: _____ ml Air _____ ml Ratio: _____
Surgeon/Laser operator	
Assistant present?	Yes <input type="checkbox"/> No <input type="checkbox"/>
Finish Time (patient off table)	
Any comments	

Please ensure patients have the analgesia diary and pain scores to complete.

A6: EVLT Technique -TRIAL – FOLLOW UP 1

Please complete for all trial patients at first follow-up appointment (**1 week**).

Also collect ANALGESIA DIARY and PAIN SCORES.

Date (today)	
Patient Details (ID label if available)	Name: DOB: Hospital number:
Side of Treatment	Left <input type="checkbox"/> Right <input type="checkbox"/>
LSV Phlebitis (clinical assessment)	Yes <input type="checkbox"/> No <input type="checkbox"/>
Time to work (if employed) in days	
Time to normal activity (days)	
Ultrasound Assessment	
Diameter LSV (while standing) in mm	2cm distal to SFJ <input type="checkbox"/> Medial to knee <input type="checkbox"/> Below-knee <input type="checkbox"/>
Echogenicity LSV	Iso <input type="checkbox"/> Hyper <input type="checkbox"/> Hypo <input type="checkbox"/>
Compressibility LSV	Not <input type="checkbox"/> Partially <input type="checkbox"/> Completely <input type="checkbox"/>
Flow LSV above-knee	No flow <input type="checkbox"/> <1sec reflux <input type="checkbox"/> >1sec reflux <input type="checkbox"/>
Flow LSV below-knee	No flow <input type="checkbox"/> <1sec reflux <input type="checkbox"/> >1sec reflux <input type="checkbox"/>
SFJ competence	Competent <input type="checkbox"/> Incompetent <input type="checkbox"/>
Complications;Eg: sensory loss, infection, haematoma (describe any and outcome)	

Thank you. Any queries please contact Nada Theivacumar, Research Fellow, Vascular Surgery Unit, LGI.

A7: EVLT Technique RCT– FOLLOW UP 2

Please complete for all trial patients at second follow-up appointment (**6 weeks**).

Date	
Patient Details (ID label if available)	Name: DOB: Hospital number:
Side of Treatment	Left <input type="checkbox"/> Right <input type="checkbox"/>
LSV Phlebitis (clinical assessment)	Yes <input type="checkbox"/> No <input type="checkbox"/>
Time to work (if employed) in days	
Time to normal activity (days)	
Complications eg neuritis, infection, haematoma (describe any and outcome)	
Injection sclerotherapy required	Yes <input type="checkbox"/> No <input type="checkbox"/>
Number of visits for sclerotherapy	

Ultrasound Assessment	Diameter LSV (while standing) in mm	2cm distal to SFJ	<input type="text"/>	Medial to knee	<input type="text"/>		
		Below-knee	<input type="text"/>				
	Echogenicity LSV	Iso	<input type="text"/>	Hyper	<input type="text"/>	Hypo	<input type="text"/>
	Compressibility LSV	Not	<input type="text"/>	Partially	<input type="text"/>	Completely	<input type="text"/>
	Flow LSV above-knee	No flow	<input type="text"/>	<1sec reflux	<input type="text"/>	>1sec reflux	<input type="text"/>
	Flow LSV below-knee	No flow	<input type="text"/>	<1sec reflux	<input type="text"/>	>1sec reflux	<input type="text"/>
	SFJ competence	Competent	<input type="text"/>	Incompetent	<input type="text"/>		

Thank you. Any queries please contact Nada Theivacumar, Research Fellow, Vascular Surgery Unit, LGI.

A8: EVLT Technique RCT – FOLLOW UP 3

Please complete for all trial patients at third follow-up appointment (**12 weeks**).

Date (today)	
Patient Details (ID label if available)	Name: DOB: Hospital number:
Side of Treatment	Left <input type="checkbox"/> Right <input type="checkbox"/>
Patient satisfaction (with overall treatment)	Very Completely satisfied _____ unsatisfied
Patient view on cosmesis	Not at all pleased _____ Very pleased
Complications eg neuritis, infection, haematoma (describe any and outcome)	
Sclerotherapy required	Yes <input type="checkbox"/> No <input type="checkbox"/>
Number of visits for sclerotherapy	
VCSS score	_____/30
CEAP Score	C_____ E_____ A_____ P_____

PLEASE TURN OVER.....

Number Days in Hospital/DCU	
Number of Outpatients Visits	
Ultrasound Assessment	2cm distal to SFJ <input type="checkbox"/> Medial to knee <input type="checkbox"/> Below-knee <input type="checkbox"/>
Diameter LSV (while standing) in mm	Iso <input type="checkbox"/> Hyper <input type="checkbox"/> Hypo <input type="checkbox"/>
Echogenicity LSV	Not <input type="checkbox"/> Partially <input type="checkbox"/> Completely <input type="checkbox"/>
Compressibility LSV	No flow <input type="checkbox"/> <1sec reflux <input type="checkbox"/> >1sec reflux <input type="checkbox"/>
Flow LSV above-knee	No flow <input type="checkbox"/> <1sec reflux <input type="checkbox"/> >1sec reflux <input type="checkbox"/>
Flow LSV below-knee	Competent <input type="checkbox"/> Incompetent <input type="checkbox"/>
SFJ competence	

Please also check:

- **Aberdeen Vein Score**
- **EuroQol**
- **Photo**

A9: EVLT Technique RCT – FOLLOW UP 4Please complete for all trial patients at third follow-up appointment (**1 year**).

Date (today)					
Patient Details (ID label if available)	Name:				
	DOB:				
	Hospital number:				
Side of Treatment	Left	<input type="checkbox"/>	Right	<input type="checkbox"/>	
VCSS score	_____/30				
CEAP Score	C	____	E	____	
	A	____	P	____	
Residual vvs? (Dr)	Yes	<input type="checkbox"/>	No	<input type="checkbox"/>	
Residual vvs? (Pt)	Yes	<input type="checkbox"/>	No	<input type="checkbox"/>	
Further Treatment? (had or awaiting – details)					
Ultrasound Assessment	2cm distal to SFJ	<input type="checkbox"/>	Medial to knee	<input type="checkbox"/>	
	Below-knee	<input type="checkbox"/>			
	Diameter LSV (while standing) in mm	Iso	<input type="checkbox"/>	Hyper	<input type="checkbox"/>
				Hypo	<input type="checkbox"/>
	Echogenicity LSV	Not	<input type="checkbox"/>	Partially	<input type="checkbox"/>
				Completely	<input type="checkbox"/>
	Compressibility LSV	No flow	<input type="checkbox"/>	<1sec reflux	<input type="checkbox"/>
				>1sec reflux	<input type="checkbox"/>
	Flow LSV above-knee	No flow	<input type="checkbox"/>	<1sec reflux	<input type="checkbox"/>
				>1sec reflux	<input type="checkbox"/>
Flow LSV below-knee	Competent	<input type="checkbox"/>	Incompetent	<input type="checkbox"/>	
SFJ competence					

CHECK: Aberdeen Vein Questionnaire complete

A10: Daily visual analogue score (pain)

Each day please mark a cross on the line in the box to show any pain you have from your varicose vein treatment. If you don't have any pain, mark a cross at the left-hand end of the line. The more severe your pain is, the further to the right you mark a cross.

Thursday (day of treatment)	No pain _____	Worst pain imaginable
Friday	No pain _____	Worst pain imaginable
Saturday	No pain _____	Worst pain imaginable
Sunday	No pain _____	Worst pain imaginable
Monday	No pain _____	Worst pain imaginable
Tuesday	No pain _____	Worst pain imaginable
Wednesd	No pain _____	Worst pain imaginable

A11: Analgesia Diary

For each day please write down how many painkillers and what painkillers you took, if any. If you didn't need to take any painkillers or if you took the painkillers for something else other than your legs (eg a headache) please leave the space blank.

	Name of Painkiller	Dose of each tablet	Number of tablets taken (over 24hrs)
Thursday (day of treatment)			
Friday			
Saturday			
Sunday			
Monday			
Tuesday			
Wednesday			

A 12: Laser vein follow-up proforma

Date of treatment	
Side treated	
Time to return to normal activity	
Analgesic requirement	
'LSV phlebitis' (Y/N)	
Injections needed (Y/N)	
Injections completed (Y/N)	
Total number of visits for injections (if completed)	
LSV scan result: 1. Mainstem? – measure length any patent vein 2. Tributaries?	
Patient view on cosmesis	
Would patient have laser therapy again?	

A13: Patient Questionnaire (one year follow-up)

Name.....

Date of Birth.....

For each question please place a tick in the box which best applies to you.

1. For each of the following symptoms please indicate whether you had these before laser treatment and whether the treatment helped make them better?

	Before Treatment		After Treatment			
	Yes	No	Gone	Improved	Same	Worse
(i) Aching or painful legs	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
(ii) Itching legs	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
(iii) Ankle swelling	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
(iv) Did you wear a support stocking?	<input type="checkbox"/>	<input type="checkbox"/>	Yes <input type="checkbox"/>	No <input type="checkbox"/>		

2. Would you describe your laser treatment overall as successful? Yes No

If not, why do you feel it was unsuccessful?.....

3. On the scale below, please mark with an "X" how satisfied you are with the results of your laser treatment:

Very Disappointed _____ Completely Satisfied

4. Did you have any problems following the laser treatment? Yes No

If so please describe:.....

3. Do you have any varicose veins now (on the same leg that was treated)? If "no" go to question 5 Yes No

4. If you do have varicose veins now, are these:
 a) new veins that have appeared since your laser treatment Yes No

b) veins that were there when you had your laser treatment Yes No

c) compared to before your laser treatment are they: Better Worse Same

5. Have you had any further treatment for varicose veins since the laser treatment? Yes No

If you have had further treatment, what did you have done?

a) injections b) an operation c) further laser treatment

Please add any details.....
.....
.....

4. If you needed treatment for varicose veins again (eg for the other leg) would you have laser treatment again? Yes No

If not, please explain why not:.....
.....
.....

5. Would you recommend laser treatment to a friend with varicose veins? Yes No

Thank you very much for your time.

Mr. Nada Theivacumar (Research Fellow)
Mr M J Gough /Mr A I D Mavor
Vascular Surgery Unit
The General Infirmary at Leeds

B1: CEAP Classification**C – Clinical Signs**

C₀: No visible or palpable signs of venous disease

C₁: Telangiectases or reticular veins

C₂: Varicose veins

C₃: Edema

C₄: Skin changes ascribed to venous disease (eg pigmentation, venous eczema, lipodermatosclerosis)

C₅: Skin changes as defined above with healed ulceration

C₆: Skin changes as defined above with active ulceration

Telangiectases are defined as dilated intradermal venules of up to a diameter of approximately 1mm, and reticular veins are defined as dilated subdermal veins up to a size of about 4mm that are not palpable.

Varicose veins are palpable, dilated subcutaneous veins usually larger than 4mm.

E – Aetiology

Congenital	E _C
Primary (undetermined cause)	E _P
Secondary (known cause – post-thrombotic, post-traumatic, other))	E _S

A – Anatomy

Superficial	A _S
Deep	A _D
Perforator	A _P

P – Pathophysiology

Reflux	P _R
Obstruction	P _O
Reflux and Obstruction	P _{R,O}

B2: Venous Clinical Severity Score

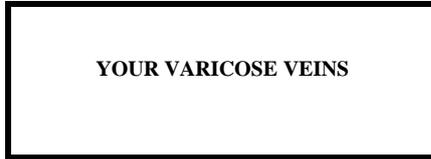
Score each attribute (0-3), then sum these scores to produce an overall score (0-30).

ATTRIBUTE	ABSENT = 0	MILD = 1	MODERATE = 2	SEVERE = 3
PAIN	None	Occasional, not restricting activity or requiring analgesics	Daily, moderate activity limitation, occasional analgesics	Daily, severe limiting activities or requiring regular use of analgesics
VARICOSE VEINS¹	None	Few, scattered: branch varicose veins	Multiple: LSV varicose veins confined to calf or thigh	Extensive: thigh and calf or LSV and SSV distribution
VENOUS OEDEMA²	None	Evening ankle oedema only	Afternoon oedema, above ankle	Morning oedema above ankle and requiring activity change, elevation
SKIN PIGMENTATION³	None or focal, low intensity (tan)	Diffuse, but limited in area and old (brown)	Diffuse over most of gaiter distribution (lower 1/3) or recent pigmentation (purple)	Wider distribution (above lower 1/3) and recent pigmentation
INFLAMMATION	None	Mild cellulitis, limited to marginal area around ulcer	Moderate cellulitis, involves most of gaiter area (lower 1/3)	Severe cellulitis (lower 1/3 and above) or significant venous eczema
INDURATION	None	Focal, circum-malleolar (<5cm)	Medial or lateral leg, less than lower 1/3 leg	Entire lower 1/3 leg or more
NO. OF ACTIVE ULCERS	0	1	2	>2
ACTIVE ULCERATION, DURATION	None	<3mths	>3mths, <1yr	Not healed >1yr
ACTIVE ULCER, SIZE⁴	None	<2cm diameter	2-6cm diameter	>6cm diameter
COMPRESSIVE THERAPY	Not used or not compliant	Intermittent use of stockings	Wears elastic stockings most days	Full compliance: stockings + elevation

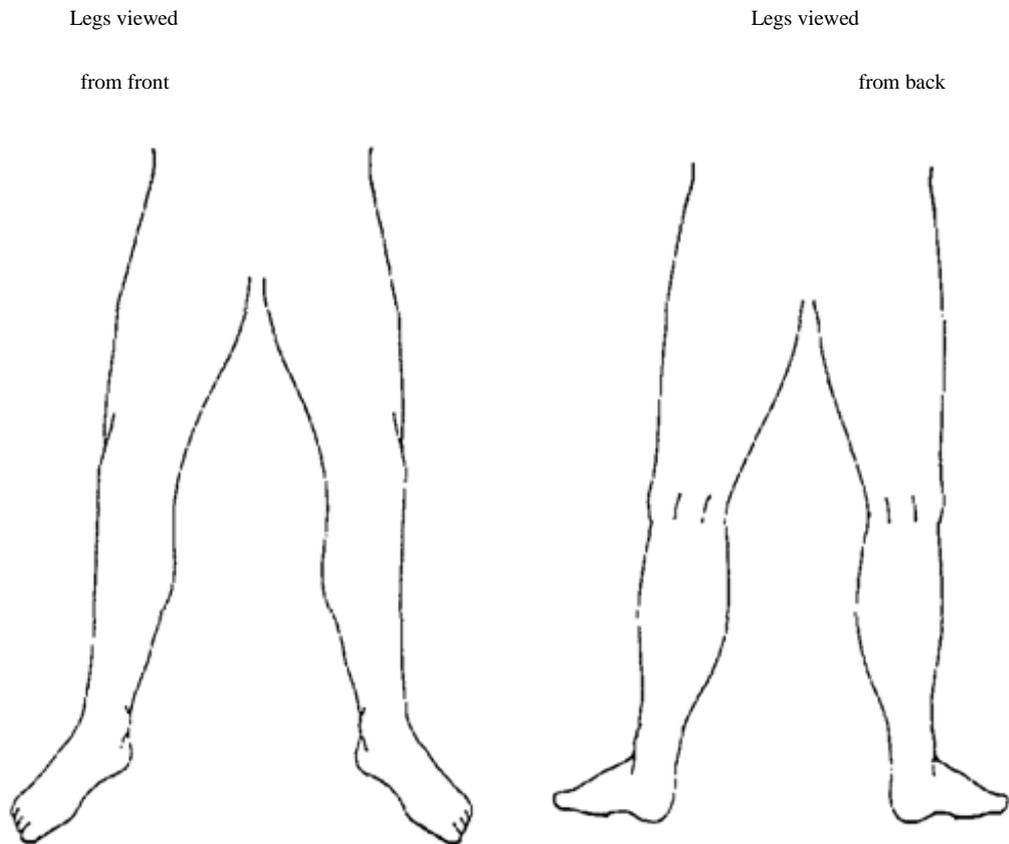
1. "Varicose" veins must be >4mm diameter to qualify so that differentiation is ensured between C1 and C2 venous pathology.
2. Presumed venous origin by characteristics (e.g. Brawny [not pitting or spongy] oedema), with significant effect of standing/limb elevation and/or other clinical evidence of venous aetiology (i.e. varicose veins, history of DVT). Oedema must be regular finding (e.g. daily occurrence). Occasional or mild oedema does not qualify.
3. Focal pigmentation over varicose veins does not qualify.
4. Largest dimension/diameter of largest ulcer.
5. Sliding scale to adjust for background differences in use of compressive therapy.

B3: Aberdeen Varicose Veins Questionnaire

(Andrew Garratt, 1996, Health Services Research Unit, Department of Public Health, University of Aberdeen)



1. Please draw in your varicose veins in the diagram(s) below:-



2. In the last two weeks, for how many days did your varicose veins cause you pain or ache?

(Please tick one box for each leg)

	R Leg	L Leg
None at all	<input type="checkbox"/>	<input type="checkbox"/>
Between 1 and 5 days	<input type="checkbox"/>	<input type="checkbox"/>
Between 6 and 10 days	<input type="checkbox"/>	<input type="checkbox"/>
For more than 10 days	<input type="checkbox"/>	<input type="checkbox"/>

3. During the last two weeks, on how many days did you take painkilling tablets for your varicose veins?

(Please tick one box)

None at all	<input type="checkbox"/>
Between 1 and 5 days	<input type="checkbox"/>
Between 6 and 10 days	<input type="checkbox"/>
For more than 10 days	<input type="checkbox"/>

4. In the last two weeks, how much ankle swelling have you had?

(Please tick one box)

None at all	<input type="checkbox"/>
Slight ankle swelling	<input type="checkbox"/>
Moderate ankle swelling (eg. causing you to sit with your feet up whenever possible)	<input type="checkbox"/>
Severe ankle swelling (eg. causing you difficulty putting on your shoes)	<input type="checkbox"/>

5. In the last two weeks, have you worn support stockings or tights?

(Please tick one box for each leg)

	R Leg	L Leg
No	<input type="checkbox"/>	<input type="checkbox"/>
Yes, those I bought myself without a doctor's prescription	<input type="checkbox"/>	<input type="checkbox"/>
Yes, those my doctor prescribed for me which I wear occasionally	<input type="checkbox"/>	<input type="checkbox"/>
Yes, those my doctor prescribed for me which I wear every day	<input type="checkbox"/>	<input type="checkbox"/>

6. In the last two weeks, have you had any itching in association with your varicose veins?

(Please tick one box for each leg)

	R Leg	L Leg
No	<input type="checkbox"/>	<input type="checkbox"/>
Yes, but only above the knee	<input type="checkbox"/>	<input type="checkbox"/>
Yes, but only below the knee	<input type="checkbox"/>	<input type="checkbox"/>
Both above and below the knee	<input type="checkbox"/>	<input type="checkbox"/>

7. Do you have purple discolouration caused by tiny blood vessels in the skin, in association with your varicose veins?

(Please tick one box for each leg)

	R Leg	L Leg
No	<input type="checkbox"/>	<input type="checkbox"/>
Yes	<input type="checkbox"/>	<input type="checkbox"/>

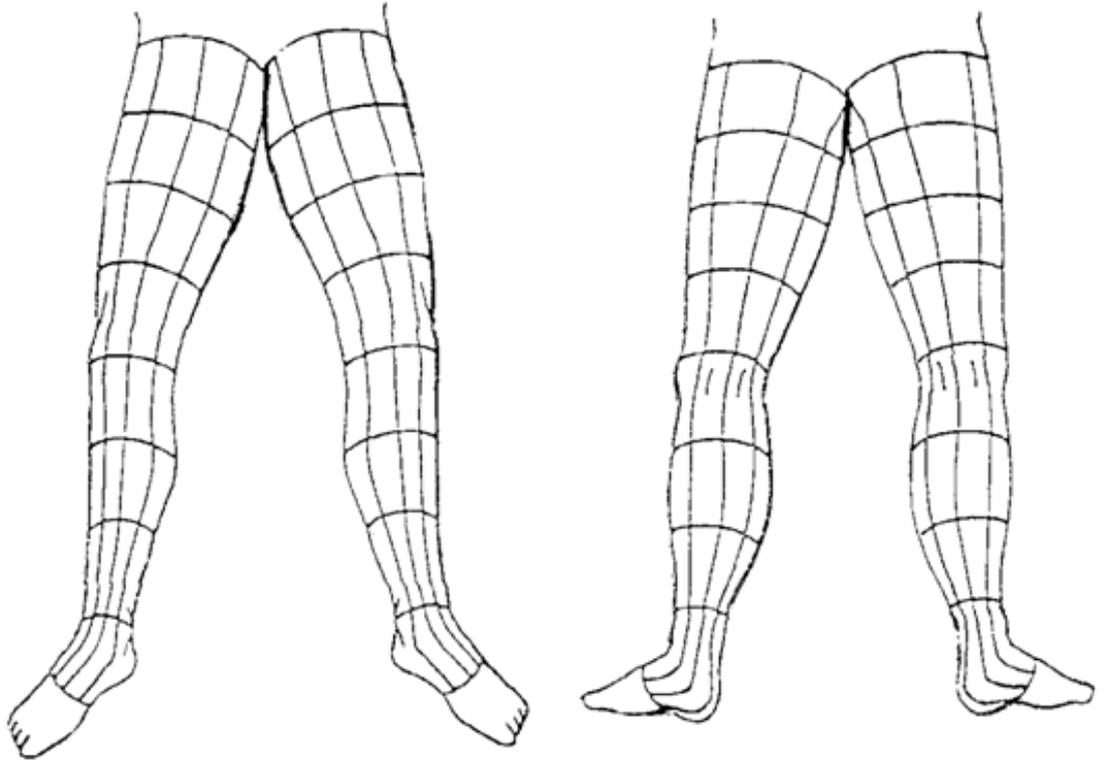
8. Do you have a rash or eczema in the area of your ankle?

(Please tick one box for each leg)

	R Leg	L Leg
No	<input type="checkbox"/>	<input type="checkbox"/>
Yes, but it does not require any treatment from a doctor or district nurse	<input type="checkbox"/>	<input type="checkbox"/>
Yes, and it requires treatment from my doctor or district nurse	<input type="checkbox"/>	<input type="checkbox"/>

9. **Do you have a skin ulcer associated with your varicose veins?**
(Please tick one box for each leg)
- | | R Leg | L Leg |
|-----|--------------------------|--------------------------|
| No | <input type="checkbox"/> | <input type="checkbox"/> |
| Yes | <input type="checkbox"/> | <input type="checkbox"/> |
-
10. **Does the appearance of your varicose veins cause you concern?**
(Please tick one box)
- | | | |
|---|----|--------------------------|
| | No | <input type="checkbox"/> |
| Yes, their appearance causes me slight concern | | <input type="checkbox"/> |
| Yes, their appearance causes me a great deal of concern | | <input type="checkbox"/> |
-
11. **Does the appearance of your varicose veins influence your choice of clothing including tights?**
(Please tick one box)
- | | | |
|--|--------------|--------------------------|
| | No | <input type="checkbox"/> |
| | Occasionally | <input type="checkbox"/> |
| | Often | <input type="checkbox"/> |
| | Always | <input type="checkbox"/> |
-
12. **During the last two weeks, have your varicose veins interfered with your work/ housework or other daily activities?**
(Please tick one box)
- | | | |
|--|----|--------------------------|
| | No | <input type="checkbox"/> |
| I have been able to work but my work has suffered to a slight extent | | <input type="checkbox"/> |
| I have been able to work but my work has suffered to a moderate extent | | <input type="checkbox"/> |
| My veins have prevented me from working one day or more | | <input type="checkbox"/> |
-
13. **During the last two weeks, have your varicose veins interfered with your leisure activities (including sport, hobbies and social life)?**
(Please tick one box)
- | | | |
|---|----|--------------------------|
| | No | <input type="checkbox"/> |
| Yes, my enjoyment has suffered to a slight extent | | <input type="checkbox"/> |
| Yes, my enjoyment has suffered to a moderate extent | | <input type="checkbox"/> |
| Yes, my veins have prevented me taking part in any leisure activities | | <input type="checkbox"/> |

Scoring grid



Recoding the Questionnaire

Question	Left Leg	Right Leg	Maximum score per question
1. Score per box	0.172	0.172	22.016
2	0 0.500 1.000 1.812	0 0.500 1.000 1.812	3.624
3	0 0.812 1.625 2.437	0 0.812 1.625 2.437	2.437
4	0 1.250 1.875		1.875
5	0 1.374 2.000 5.496	0 1.374 2.000 5.496	10.992
6	0 1.374 1.437 2.748	0 1.374 1.437 2.748	5.496
7	0 2.000	0 2.000	4
8	0 2.624 6.121	0 2.624 6.121	12.242
9	0 9.118	0 9.118	18.236
10	0 1.625 3.249 5.248		5.248
11	0 1.625 2.624 3.998		3.998
12	0 1.625 3.373 5.496		5.496
13	0 1.625 2.437 3.998		3.998
		Maximum possible score	99.658 ^a

^aDue to rounding errors the maximum possible score does not reach 100.

Total word Count including reference excluding appendix is 46,841.

Total number of tables excluding appendix: 37

Total number of Figures excluding appendix: 45

Appendix C: Ethical Approval for the RCT: Chapter 5

This is attached in pages from 259-260

19 September 2005

Research & Development Directorate
6th Floor, Wellcome Wing

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Leeds General Infirmary

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→ MOIRA / NIKKI
TO KEEP
SAFE PLEASE

Mike

Dear Mr Gough

Re: LTHT R&D Approval of Project No VS05/7137: Randomised controlled trial of standard EVLT versus standard EVLT with below-knee foam sclerotherapy versus above and below-knee EVLT for varicose veins

I write with reference to the above research study. I can now confirm that this study has R&D approval and the study may proceed at The Leeds Teaching Hospitals NHS Trust (LTHT). This organisational level approval is given based on the information provided in the Research Ethics Committee and Trust R&D Project Approval form.

As principal investigator you have responsibility for the design, management and reporting of the study. In undertaking this research you must comply with the requirements of the *Research Governance Framework for Health and Social Care* which is mandatory for all NHS employees. This document may be accessed on the Department of Health website at <http://www.dh.gov.uk/PolicyAndGuidance/ResearchAndDevelopment/>

R&D approval is therefore given on the understanding that you comply with the requirements of the *Framework* as listed in the attached sheet "Conditions of Approval".

If you have any queries about this approval please do not hesitate to contact the R&D Department on telephone 0113 392 2878.

Indemnity Arrangements

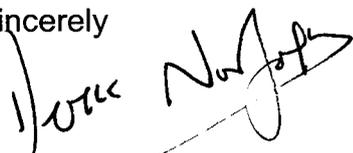
The Leeds Teaching Hospitals NHS Trust participates in the NHS risk pooling scheme administered by the NHS Litigation Authority 'Clinical Negligence Scheme for NHS Trusts' for: (i) medical professional and/or medical malpractice liability; and (ii) general liability. NHS Indemnity for negligent harm is extended to researchers with an employment contract (substantive or honorary) with the Trust. The Trust only accepts liability for research activity that has been managerially approved by the R&D Department.

Chairman Martin Buckley Chief Executive Neil McKay CB

The Leeds Teaching Hospitals Incorporating: Chapel Allerton Hospital Cookridge Hospital Leeds Chest Clinic
Leeds Dental Institute Seacroft Hospital St James's University Hospital The General Infirmary at Leeds
Wharfedale Hospital

The Trust therefore accepts liability for the above research project and extends indemnity for negligent harm to cover you as principal investigator and the researchers listed on the R&D approval form provided that each member of the research team has an employment contract (substantive or honorary) with the Trust. Should there be any changes to the research team please ensure that you inform the R&D Department and that s/he obtains an employment contract with the Trust if required.

Yours sincerely

A handwritten signature in black ink, appearing to read "Dr D R Norfolk". The signature is written in a cursive style with a large, sweeping flourish at the end.

Dr D R Norfolk
Associate Director of R&D