OPTIMISING OUTCOMES IN THE TREATMENT OF LOWER LIMB VARICOSE VEINS

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CORRECTIONS PAGE

1. A list of abbreviations has been added to the thesis. (Page 16)

2. The list of full publications associated with this thesis has been divided into 2 – publications arising directly from the thesis, and subsequent publications arising from the work of this thesis (page 30)

3. Proper nomenclature has been used for the great saphenous and small saphenous vein, and reference included for this (page 40)

4. A section has been included to mention the use of radiofrequency ablation (RFA) as an option for endovenous management of varicose veins (page 61)

5. Legends for tables and figures have been expanded

6. Spelling mistakes and omissions have been corrected

7. Text has been introduced to clarify the number of patients and limbs assessed in the results of study 3 (page 108)

8. Text has been introduced to specify “major complications” in the results of study 3 (page 113)

9. Clarification has been made on the duration of EVLTAP procedure to (page 148)

10. The section on critique has been removed, and the critique has been incorporated in the discussion of the relevant study.

11. Appendices have been added at the end to show the VCSS, AVVQ and SF 36 forms

ABSTRACT

Varicose veins are dilated and tortuous subcutaneous veins, which affect a significant proportion of adults. They cause physical and emotional symptoms, and affect quality of life in sufferers. The management of varicose veins has evolved since the early 20th century, when Babcock described what has now become the gold standard surgical treatment. Perhaps the most significant evolution is the development and popularisation of minimally invasive therapy, especially endovenous laser ablation (EVLA) in the last two decades. This thesis focuses on the optimisation of outcomes in the management of this very common condition.

Four studies were performed to evaluate varicose vein treatment modalities and outcomes, investigating key issues such as: the proportion of patients suitable for EVLA; optimisation of EVLA; how does EVLA compare with surgery, and what is the effect of prophylactic antibiotics on wound complications following surgery? Approximately 60% of varicosities are suitable for EVLA, with vein anatomy being the commonest cause for unsuitability. The concomitant performance of phlebectomies at the time of EVLA was shown to be feasible, acceptable to patients, and improved outcomes. EVLA was shown to be clinically effective, and eliminated the early quality of life limitations of surgery. Wound complications following surgery were found to be significantly reduced by the use of prophylactic antibiotics.

LIST OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

GLOSSARY OF ABBREVIATION

95% CI	95% confidence interval
ALTV	Anterior lateral thigh vein
ASEPSIS	Wound scoring system (see text)
AVVQ	Aberdeen varicose veins questionnaire
BMI	Body mass index
CEAP	Clinical aEtiologic Anatomic Pathophysiolic Score
CVI	Chronic venous insufficiency
DUS	Duplex ultrasound
DVT	Deep vein thrombosis
EVLA	Endovenous laser ablation
EVLT	Endovenous laser therapy (synonymous with EVLA)
EVLTAP	Endovenous laser therapy with concomitant ambulatory phlebectomy
g	gram - unit of weight (may be

	prefixed by k - kilo, m - milli)
GA	General anaesthetic
GP	General Practitioner
GSV	Great saphenous vein
IQR	Inter-quartile range
J	Joule - unit of energy
L	Litre - unit of volume (may be prefixed by m - milli)
LA	Local anaesthetic
M	Metre - unit of length (may be prefixed by c - centi, m - milli, n - nano)
MMP	Matrix metallo prateinase
NHS	National Health Service
OR	Odds ratio
QoL	Quality of life
RCT	Randomised Clinical (controlled) Trial
RFA	Radiofrequency Ablation
SFJ	Sapheno Femoral Junction

SF36	Short form 36 (Domains: PF-Physical Function; RP-Physical Role; BP-Bodily Pain; GH-General Health; Vit-Vitality; SF-Social Function; RE-Emotional Role; MH-Mental Health
SPJ	Sapheno popliteal junction
SSI	Surgical site infection
SSV	Small saphenous vein
STD	Sodium tetradecyl sulphate
TIMP	Tissue inhibitor of Matrix Metallo Proteinases
VAS	Visual analogue scale
VCSS	Venous clinical severity score

SUMMARY OF THESIS

Introduction

Varicose veins are dilated, tortuous, and palpable subcutaneous veins. They are common and affect up to a third of adults in the Western world. Varicose veins cause symptoms and complications, cosmetic concerns, but more importantly, cause health - related quality of life limitations. The gold standard treatment of varicose veins is surgery. Babcock introduced surgery for lower limb varicose veins in the early 1900s, and since then the procedure has undergone various modifications and evolved to become a clinically effective therapy for varicose veins. It improves quality of life, and could be cost effective in the day case setting. There are however complications and limitations to standard surgery, including the need for a general anaesthetic in most cases, as well as wound related issues.

In the mid to late 1990s, there was a major breakthrough in the treatment of varicose veins with the introduction of minimally invasive options. Arguably, the greatest revolution in these options has been with endovenous laser ablation (EVLA) first described by Bone et al. This uses diode laser energy to cause thermal destruction of the vein from within, resulting in a non thrombotic occlusion. The procedure has proven to be safe, effective and associated with minimal significant complications, and compares very favourably with surgery. Moreover, it

can be performed in the office setting under local tumescent anaesthetic. One minor “set back” of laser therapy is the requirement for subsequent adjunctive therapies in 30% - 99% of patients, to deal with branch varicosities. Also not every varicose vein may be suitable for laser ablation.

This thesis focuses on a number of issues which are key to the optimisation of lower limb varicose vein treatment:

What proportion of patients with varicose veins can undergo EVLA?

How can EVLA be optimised for efficacy, reduce the need for subsequent procedures, and yet preserve the excellent patient experience?

How does EVLA compare with surgery?

Can the use of prophylactic antibiotics reduce wound complications following surgery for varicose veins, thereby eliminating one significant problem with standard surgery?

Methods

Four related trials were designed to investigate these issues. The EVLA suitability study interrogated the waiting list for day - case varicose vein surgery and carried out venous doppler ultrasound on 150 randomly selected patients, based on very rigid suitability criteria, which were derived from a review of the then current

literature on EVLA practice. A prospective review of the waiting list for vv surgery in a university hospital was performed between June 2004 and May 2005. The period represented the first year of commencement of EVLA at the centre. I50 sequentially selected patients listed for unilateral primary sapheno femoral junction (SFJ) ligation, stripping of the GSV and avulsions were invited for duplex ultrasound scan (DUS) to assess suitability for EVLA. Suitability criteria included: Isolated SFJ / GSV incompetence, absence of major incompetent thigh branch, peri genicular GSV diameter greater than 5mm, as well as patient acceptance of local anaesthetic procedure.

The second study was a prospective observational study investigating the feasibility of performing concomitant ambulatory phlebectomy / avulsions along with EVLA under tumescent anaesthetic (a procedure were termed EVLTAP). 67 patients (70 limbs) with varicosities of the great saphenous vein, confirmed by duplex scan (DUS) underwent EVLTAP. Pain severity was assessed on days 1, 4 and 7 using a visual analogue scale (VAS) of 0 to 10. Clinical and DUS assessments were carried out at 1, 6 and 12 weeks (no DUS at 6 weeks). Residual varicosities were managed by re-do phlebectomy or sclerotherapy. Patients' satisfaction with cosmetic appearance and with the overall treatment procedure was assessed at 3 months using a VAS rating between 0 and 10.

Study three was a non randomised trial comparing standard surgery with EVLA. Two non-randomised groups were studied. The EVLA group comprised 70 patients, median age 49 (inter quartile range [IQR] 35-58) years. The surgery group was comprised of 62 patients, median age 49, (IQR 35-61) years. Patients were assessed prior to, and at 1, 6, and 12 weeks post-procedure using the following quality of life and clinical assessment tools: Short Form 36 (SF36), Aberdeen Varicose Veins Questionnaire (AVVQ), and the Venous Clinical Severity Score (VCSS).

The final study was a randomised controlled trial investigating the effect of a single dose of antibiotic in preventing groin wound complications in patients undergoing varicose vein surgery. 443 patients undergoing varicose vein surgery randomly received a single prophylactic dose of 1.2g co-amoxiclav (219 patients) or no antibiotic (224 patients). Patients completed a wound diary on postoperative days 3, 5, 7, 9 and 10 using an adapted ASEPSIS method of postoperative wound assessment, and were reviewed at 14 days.

Results

Study 1: 482 patients were added to the waiting list (328 women). 339 were listed for GSV surgery. Of those invited for DUS, 112 (74.6%) attended. 63 patients (56%) were suitable, while 49 (44%) were unsuitable.

Of unsuitable patients, 39% had incompetent thigh branch, 20% had peri genicular GSV less than 5mm, 12% wanted general anaesthetic and 2% preferred surgery. 1 patient (2%) had no SFJ/GSV incompetence on DUS, and 24% were unsuitable for combined reasons.

Study 2: 49 patients (70%) completed 12 weeks follow up. Median pain scores were 1.6 (IQR 0.2-4.8), 0.3 (0–1.4) and 0.2 (0–1.1) on days 1, 4 and 7 respectively. DUS demonstrated 69 (99%) and 47 (96%) occluded GSVs at 1 week and 3 months respectively. Subsequent sclerotherapy or phlebectomy was performed on 3 (4%) or 1 (1%) limbs respectively. Cosmetic satisfaction was 9.6 (median; IQR 8.9–10) and overall satisfaction 9.8 (IQR 9.3–10).

Study 3: Follow up at 1, 6 and 12 weeks was 100%, 77% and 70% following EVLT and 100%, 85% and 47% following surgery.

SF36 scores were significantly better in the EVLA group at 1 week, (Physical Functioning, Role Physical, Bodily Pain, Vitality and Social Functioning domains) and at 6 weeks (Physical Functioning and Role Physical). At 12 weeks, no significant differences were evident between the groups.

AVVQ scores were significantly better in the EVLA group at 6 and 12 weeks. VCSS scores were significantly improved in both groups at 12 weeks.

Study 4: Both groups were balanced at baseline. Patients receiving antibiotic prophylaxis had lower ASEPSIS wound scores on days 3, 5 and 7 (p=0.043, 0.032 and 0.003 respectively), and lower total ASEPSIS scores (median [IQR] of 3 [0-9] versus 6 [0-15]; p=0.013). They were also less likely to consult their General Practitioner (16% vs. 24.3%; p=0.040) and receive antibiotics (4.7% vs. 13.5%%; p=0.002) postoperatively for wound related problems. Wound outcomes were worse with higher body mass index (BMI) (Odds Ratio [OR] 0.92, 95% CI 0.87-0.97; p=0.005), and current smoking (OR 0.5, 95% CI 0.3-0.9, p=0.03). Receiving prophylactic antibiotic conferred satisfactory wound healing (OR 2.2, 95% CI=1.3-3.6; p=0.003).

Conclusions

The management of varicose veins has evolved since the 1900s. The last two decades have especially seen a tremendous advancement in management of varicose veins, particularly in endovascular techniques. The studies included in this thesis have explored important aspects of varicose vein management. At the time of performing the studies, just over half of all patients listed for primary varicose vein surgery were suitable for EVLA. As anticipated however, expertise has grown, indications have been expanded and more patients are now being offered EVLA and other minimally invasive treatments.

The EVLTAP procedure was designed to take away a clear limitation of EVLA in its early years: the need for subsequent interventions in the majority of patients. EVLTAP produced excellent results, was found feasible and acceptable, and clearly obviated the need for subsequent procedures in the short-term.

EVLA and surgery provide similar Quality of Life and clinical improvements in patients with varicose veins. Standard surgical treatment of varicose veins however, is associated with QoL limitations in the early postoperative period. EVLA has been shown to remove the QoL limitations experienced by patients in the early surgical postoperative period.

Another limitation of standard surgery is the risk of wound complications including infection. Antibiotic prophylaxis reduces wound-related problems following varicose vein surgery, and reduces the burden placed upon primary care by patients presenting with postoperatively wound problems.

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AUTHOR'S DECLARATION

'I confirm that this work is original and that if any passage(s) or diagram(s) have been copied from academic papers, books, the internet or any other sources these are clearly identified by the use of quotation marks and the reference(s) is fully cited. I certify that, other than where indicated, this is my own work and does not breach the regulations of HYMS, the University of Hull or the University of York regarding plagiarism or academic conduct in examinations. I have read the HYMS Code of Practice on Academic Misconduct, and state that this piece of work is my own and does not contain any unacknowledged work from any other sources'.

FULL PUBLICATIONS ASSOCIATED WITH THESIS

Publications directly arising from this thesis

Mekako AI, Hatfield J, Bryce J, Lee D, McCollum PT, Chetter I. A non randomised controlled trial of endovenous laser therapy and surgery in the treatment of varicose veins. *Ann Vasc Surg* 2006; 20(4): 451 -7

Mekako AI, Hatfield J, Bryce J, Heng M, Lee D, McCollum P, Chetter I. Combined endovenous laser therapy and ambulatory phlebectomy: refinement of a new technique. *Eur J Vasc Endovasc Surg* 2006; 32(6): 725 - 9

Mekako AI, Chetter I. Cutaneous hyperpigmentation after endovenous laser therapy: a case report and literature review. *Ann Vasc Surg* 2007; 21(5): 637 - 9

Mekako AI, Chetter IC, Coughlin PA, Hatfield J, McCollum PT, Hull Antibiotic pRophylaxis in Varicose vEin Surgery Trialists (HARVEST). Randomised clinical trial of co-amoxiclav versus no antibiotic prophylaxis in varicose vein surgery. *Br J Surg 2010*; 97(1): 29 – 36

Subsequent publications associated with work from this thesis

Carradice D, **Mekako AI**I, Hatfield J, Chetter IC. Randomised clinical trial of concomitant or sequential phlebectomy after endovenous laser therapy for varicose veins. Br J Surg 2009; 96(4): 369 - 75

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Carradice D, **Mekako AI**I, Mazari FA, Samuel N, Hatfield J, Chetter IC. Randomised clinical trial of endovenous laser ablation compared with conventional surgery for great saphenous varicose veins. *Br J Surg* 2011 98(4): 501 - 10

Carradice D, **Mekako AI**I, Mazari FA, Samuel N, Hatfield J, Chetter IC. Clinical and technical outcomes from a randomised clinical trial of endovenous laser ablation compared with conventional surgery for great saphenous varicose veins. *Br J Surg* 2011 98(8): 1117 - 23

1. INTRODUCTION

Varicose veins are elongated, dilated and tortuous veins. They are defined as dilated palpable subcutaneous veins, generally larger than 4mm in the upright position (Porter and Moneta 1995). The word ‘varicose’ is derived from the Latin word ‘varix’, which means twisted. The adoption of the erect position by man is thought to have greatly influenced the development of venous diseases of the lower limbs. Impairment of return of venous blood to the heart against gravity as a result of the erect position, results in the development of acute venous thrombosis, varicose veins, and chronic venous insufficiency (van den Bremer and Moll 2010). Varicose veins have been recognised for thousands of years, being mentioned in the papyrus of Ebers around 1550BC and also by Hippocrates the father of modern medicine.

1.1. Incidence and Epidemiology

Venous disease, including varicose veins, is common in industrialized and Western populations (Beebe-Dimmer, Pfeifer et al. 2005). The prevalence of varicose veins is very low in African, Asian and Australasian Aboriginal populations, although immigrants from these regions generally take on the same risk level as their host environment (Carpentier and Priollet 1994).

The estimates of varicose veins prevalence varies very widely from 2% - 56% in men and <1% - 73% in women (Beebe-Dimmer, Pfeifer et al. 2005). This variation is based, not only on real predisposing causes (which will be addressed later on), but also on differences in definitions and study methodology. In the late 1990s in the United Kingdom, the Edinburgh vein study found a prevalence of 39.7% in men and 32.2% in women (Evans, Fowkes et al. 1999). This figure is still widely quoted in current literature.

1.2. Aetiology

The Aetiology of varicose veins is unclear, although more understanding of the pathogenesis has been made in recent years. The pathogenesis of varicose veins is discussed later in this section. There are recognized factors which predispose to, or are associated with varicose veins. Perhaps the most important of these factors are sex, age, family history, and pregnancy (Lim and Davies 2009). These and other risk factors, as well as the evidence for them are discussed below.

Sex

There is no consistency in the literature as to gender differences in prevalence of varicose veins. Several studies have shown that varicose veins appear to be more prevalent in women (Brand, Dannenberg et al. 1988, Callam 1994, Bergan, Schmid-Schonbein et al. 2006). This finding is however not supported by other population based studies, which have shown higher prevalence in men (Evans,

Fowkes et al. 1999). Prevalence studies carried out among patients presenting to hospital with varicose veins, show a higher prevalence in women, and this has been explained by the fact that women are more likely than men, to report varices and present to their doctors, (Beale and Gough 2005, Beebe-Dimmer, Pfeifer et al. 2005). The Edinburgh vein study (Evans, Fowkes et al. 1999), the Italian 24 Cities Cohort study (Chiesa, Marone et al. 2005), and a Bulgarian cross sectional survey (Zahariev, Anastassov et al. 2009) showed a higher prevalence of telangiectasia in women, but a higher prevalence of trunk varicosities in men. This would indicate that perhaps, it is the presence of telangiectasia as opposed to trunk varices, which makes varicose veins more common in women. That said, there have been studies which showed no sex differences in varicose vein prevalence (Franks, Wright et al. 1992, Komsuoglu, Goldeli et al. 1994).

In studies which support a higher prevalence in women, it is presumed that pregnancy is a major contributory factor (Stansby 2000). Some evidence suggests that parous women have a higher incidence of varicose veins compared with nulliparous women, and that multiparous women have the highest risk for the development of varicose veins (Dindelli, Parazzini et al. 1993, Jukkola, Makivaara et al. 2006). More recent evidence however, has not supported this. In a study of 583 extremities in women with uncomplicated primary varicose veins (previous varicose vein surgery and history venous thrombosis excluded), Englehorn and

colleagues performed colour duplex ultrasound scans and analysed their findings as a function of number of pregnancies. There was no significant association between parity and the presence of primary varicose vein (Engelhorn, Cassou et al. 2010).

Pregnancy is associated with a number of physiologic changes which likely contribute to the development of venous distension and potentially varicose veins. The significant increase in blood volume during early pregnancy (Bernstein, Ziegler et al. 2001) increases the strain on venous capacitance, which may lead to venous dilatation. As pregnancy advances, there is increased intra abdominal pressure and impedance of central venous return arising from foetal growth and weight gain (Chapman, Abraham et al. 1998). This may also contribute to the increased prevalence of varicose vein in pregnancy. It has been observed however, that varicose veins often develop in pregnancy prior to any significant increase in uterine size (Beebe-Dimmer, Pfeifer et al. 2005). This may therefore suggest that other factors besides pressure from the gravid uterus may be important. The effect of increased levels of hormones in pregnancy is an important one. The hormones relaxin, oestrogen and progesterone (Vin, Allaert et al. 1992, Chapman, Abraham et al. 1998, Lenkovic, Cabrijan et al. 2009) are the principal players in this respect, having effects on venodilatation, venous stasis, valvular dysfunction, and possibly weakening the integrity of venous wall.

Geography and Race

Varicose veins are generally more prevalent in more developed, industrialised countries than in underdeveloped countries (Beebe-Dimmer, Pfeifer et al. 2005). A study from the late 1960s found that varicose veins were 5 times more prevalent in England than in Egypt (Mekky, Schilling et al. 1969). Although migrant populations generally take on the risk levels of their host countries (Carpentier and Priollet 1994), studies from multi-ethnic populations show a significant difference in prevalence rates among different ethnic groups. The San Diego population study (Criqui, Jamosmos et al. 2003) for example, showed a higher prevalence of visible varices in non Hispanic Whites, than in Hispanics, African-Americans, and Asians. The underlying cause for the racial and geographic variation is yet to be elucidated, but may relate to genetic factors affecting vein wall integrity.

Age

There is universal agreement that the prevalence of venous disease increases with increasing age (Evans, Fowkes et al. 1999, Beebe-Dimmer, Pfeifer et al. 2005, Chiesa, Marone et al. 2005). It is most likely that the increasing prevalence with age is the result of increased pressure on superficial veins due to the weakening of calf muscles coupled with the gradual deterioration of vessel walls over time (Beebe-Dimmer, Pfeifer et al. 2005). In addition to varicose veins, the prevalence of chronic venous insufficiency also increases with age, especially noticeable in men (Fowkes, Evans et al. 2001). Brand et al (1988) found in their survey in the

USA, that the prevalence of varicose veins among people younger than 30 years was less than 1% for men and less than 10% for women. However, from age 70 years and older, the estimates increased substantially to 57% and 77%, in men and women respectively.

Family History and Genetics

There is some evidence to support genetic and familial predisposition to varicose vein development. The risk of developing varicose veins has been reported to be 90% if both parents suffered from this disease, 25% for men and 62% for women with one affected parent and 20% when neither parent was affected (Cornu-Thenard, Boivin et al. 1994).

Although no specific genes have been identified, studies have described familial aggregation of manifestations of venous disease (Arnoldi 1958, Berard, Abenhaim et al. 2002, Lee, Evans et al. 2003). In a study of Japanese women, 42% of subjects with varicose veins reported a positive family history compared with just 14% of women without disease (Hirai, Naiki et al. 1990). In a Finnish study of 40 – 60 year old men and women with varicose veins, the odds ratio associated with self-reported positive family history, was 4.9 (Laurikka, Sisto et al. 2002). The finding was similar in a Turkish study, which noted an overall risk ratio of 4.4 associated with a positive family history (Komsuoglu, Goldeli et al. 1994).

These results have to be interpreted with some degree of caution. Firstly, most have been based on self reporting, with no independent researcher verification (Beebe-Dimmer, Pfeifer et al. 2005). Secondly, there may be recall bias, and people with venous disease are more likely to give a family history, but also more likely to display a higher proportion of misclassification and false positive report (Ahti, Makivaara et al. 2010). There is a hereditary component of varicose veins, but the effect is in all likelihood, much less than reported in literature (Ahti, Makivaara et al. 2009).

Obesity

Several studies have shown that obesity is a risk factor for development of varicose veins. Although some studies have found this effect in both men and women (Abramson, Hopp et al. 1981, Callam 1994, Sisto, Reunanen et al. 1995), the effect appears to be more so in women (Brand, Dannenberg et al. 1988, Kontosic, Vukelic et al. 2000, Lee, Evans et al. 2003). Obese women (BMI ≥ 30 Kg/m^2) were 3 times more likely to report varicose veins, according to a retrospective cohort Dutch study (Seidell, Bakx et al. 1986).

The exact pathogenic mechanism for the effect of obesity on the development of varicose veins has not been defined. The effect may be due to the increased intra abdominal pressure in the obese (Noblett, Jensen et al. 1997), which results in decreased blood flow in pelvic veins, and therefore increased lower limb venous

pressures (Fowkes, Lee et al. 2001). This is supported by a recent study in New Zealand which showed worse venous filling index (a good marker of reflux on air plethysmography) in the obese population, especially in women (van Rij, De Alwis et al. 2008). It has also been suggested that since the effect of obesity is more profound in women, there may be a confounding effect of pregnancy and parity or to the effect of circulating hormones (Lee, Evans et al. 2003, Beebe-Dimmer, Pfeifer et al. 2005). In a study of postmenopausal women in Italy however, the higher prevalence of varicose veins in obese women, was found to be independent of sex hormone levels (Iannuzzi, Panico et al. 2002).

Other risk factors

There are other risk factors associated with varicose veins, although these may not be as important as the factors discussed above, and evidence for them is at best tenuous. These factors include:

Sedentary occupations and those associated with prolonged standing (Stvrtinova, Kolesar et al. 1991)

Low fibre “Western type” diets result in constipation, straining at stool, and high venous pressure (Burkitt, Townsend et al. 1976). The Edinburgh vein study found lower fibre intake, longer intestinal transit time and straining at stool were associated with an increased risk of trunk varices, but only in men (Fowkes, Lee et al. 2001)

Height was associated with a positive risk for varicose veins (Franks, Wright et al. 1992, Laurikka, Sisto et al. 2002, Lee, Evans et al. 2003). This may be related to increased hydrostatic pressure.

Smoking (Gourgou, Dedieu et al. 2002), history of high blood pressure (Clark, Harvey et al. 2010), use of hormone replacement therapy (Jukkola, Makivaara et al. 2006), lower limb fracture (Lindhagen, Bergqvist et al. 1985) are some of the other risk factors that have been associated with the development of varicose veins.

1.3. Pathology

Anatomy of the lower limb venous circulation

The detailed anatomy of the lower limb venous circulation is well presented in anatomy texts and is not included in this work. However, a brief description is outlined below. There are 3 systems of veins that drain the lower limb: the superficial, deep, and perforator systems.

The Superficial veins are located in the superficial compartment of the limb, external to the deep fascia. It is a low pressure compartment, and the veins of this compartment drain the skin and superficial tissues. The 2 main veins of this system in the lower limbs, are the great saphenous vein (GSV; previously referred to as the long saphenous or greater saphenous vein), and the small saphenous vein

(SSV; previously referred to as the short or lesser saphenous vein).The change in nomenclature was agreed by an international interdisciplinary consensus committee in Rome, in September 2001, to eliminate confusion over previous nomenclature (Caggiati, Bergan et al. 2002). The GSV commences from the medial side of the dorsal venous arch of the foot and ascends in front of the medial malleolus, running upwards on the medial side of the leg. It passes behind the knee and curves forward along the antero-medial thigh, and perforates through the saphenous opening in the deep fascia to join the femoral vein in the upper thigh.

The SSV arises from the lateral side of the dorsal venous arch of the foot, and runs upwards, behind the lateral malleolus. It follows the lateral border of the tendo calcaneus and then runs up the middle of the back of the leg. It pierces the deep fascia, passing between the 2 heads of the gastrocnemius muscle to join the popliteal vein anywhere between the back of the knee and the upper posterior thigh. It may also terminate by joining the GSV. There are several anastomotic branches that run upward and medially from the SSV to join the GSV.

The Deep veins are located deep to the deep fascia, and run with the main arteries (known as venae comitantes). They drain the muscles and deeper tissues, and provide the vast majority of venous drainage of the lower extremity. The venae comitantes of the anterior and posterior tibial arteries join in the calf to form the

popliteal vein, which ascends to become in turn, the superficial femoral vein, the common femoral vein, then iliac vein and inferior vena cava.

Perforator veins pierce the deep fascia and connect the superficial to the deep system. They have valves that allow blood to flow from the superficial to deep systems. A few named perforating veins are fairly constant in location and are named only as vague groupings. The old nomenclature included Hunter's perforator in the mid thigh, Dodd's perforator in the distal thigh, Boyd's perforator at the knee, and Cockett's perforators in the distal medial calf and ankle.

Calf pump mechanism

The passage of blood upward from the feet against gravity depends on a complex array of valves and pumps. Muscle pumps of the calf and foot provide the motive force for venous return. This is frequently called the calf muscle pump or musculo-venous pump and is thought to function as the peripheral heart. The pump of the calf muscle chamber is the gastrocnemius and soleus muscles. There is a network of very distensible thin-walled veins within the muscles. Each segment of the calf muscle pump works in the same way as the hand bulb of a sphygmomanometer. Inflow to a segment of deep vein is through intake valves from perforating veins as well as from the deep vein segment below. Outflow is through an outflow valve to the deep vein segment above. Squeezing of the vein segment occurs when muscle

contraction (muscular systole) increases the pressure within a fascial muscle compartment. The valves of the perforator veins close to prevent blood from passing into the superficial veins, therefore blood is squeezed upwards in the deep veins, towards the heart. When the muscles relax (muscular diastole), the pressure in the deep muscular compartment and the deep veins is temporarily lower than that in the superficial compartment; blood therefore flows from the superficial to the deep veins through the perforators. Upon the next muscle contraction, the valves in the perforating veins close again, and blood is squeezed upwards in the deep veins towards the heart.

When the normal lower limb venous circulation is disturbed, varicose veins and chronic venous insufficiency result. The problem may affect the superficial, deep or perforator systems either singly or in combination. The prevailing theory is that valve reflux is important in the development of varicose veins. With valve reflux, there is retrograde flow of blood, causing venous stasis and hypertension, and vein wall dilatation, although the exact sequence in which these features occur is still subject to debate.

Pathogenesis

There is universal agreement that valve reflux is the principal determinant of varicose veins and chronic venous insufficiency (Beebe-Dimmer, Pfeifer et al.

2005). There is however no consensus as to whether primary valve incompetence is the initiating event in the pathogenesis, or is the result of vein wall dilatation. The evidence for each of these factors is examined below:

Primary valvular dysfunction

It is generally accepted that valve dysfunction with reflux leads to progressive venous insufficiency. One hypothesis proposes that the initiating event is valvular dysfunction, which causes reflux. Reflux then causes blood stasis and venous hypertension, which in turn damages the vein wall, leading to weakness and dilatation (Lim and Davies 2009). Reflux may occur in venous tributaries in the absence of axial reflux in the truncal, deep or perforator veins (Labropoulos, Kang et al. 1999). It has also been shown that primary venous reflux in both the superficial and deep veins can occur in an ascending (rather than retrograde) fashion, and can be local or segmental (Labropoulos, Giannoukas et al. 1997). These findings would indicate that saphenous vein reflux is not needed for primary varicose vein pathology to occur. Histology of valves from varicose veins show abnormalities / deformities and hypotrophy more frequently than valves from non-varicose veins (Corcos, De Anna et al. 2000). Valves from varicose veins also contain less collagen and greater inflammatory activity than valves from adjacent non varicose vein segments (Psaila and Melhuish 1989, Ono, Bergan et al. 1998).

These findings suggest a role for primary valvular dysfunction in the initiation of varicose veins.

Primary wall dilatation

An alternative hypothesis than that above, is that the formation of varicose vein is secondary to defects in cellular and extracellular matrix components, which cause weakness and altered venous tone (Raffetto and Khalil 2008). This hypothesis is supported by several clinical and biochemical / histological findings. Reflux and varicose veins do not always start at the sapheno femoral or sapheno popliteal junctions and progress in a retrograde fashion. Therefore the same argument proposed for primary vein dysfunction may actually support the role of primary vein wall dilatation, as anterograde or ascending progression of disease is more likely to be caused by primary vein wall changes leading to secondary valve incompetence, than the other way round (Lim and Davies 2009). Also varicosities are frequently observed below competent valves, and venous dilatation is seen distal to a valve, rather than proximal, which would be the case if valvular incompetence preceded wall dilatation (Naoum, Hunter et al. 2007). Structurally, changes in the vein wall media, including smooth muscle cell proliferation, and extracellular matrix degradation are observed more commonly in varicose than in non-varicose veins (Aunapuu and Arend 2005, Elsharawy, Naim et al. 2007). Studies have also found an imbalance in the collagen:elastin ratio in both varicose and adjacent non

varicose segments of saphenous vein, compared with normal saphenous vein. These changes occurred prior to valve insufficiency (Gandhi, Irizarry et al. 1993, Wali, Dewan et al. 2003).

The degradation of the extracellular matrix, which provides a structural framework of collagen, proteglycans, elastin, glycoproteins and fibronectin in which various cellular components are embedded, is likely to contribute to the weakening and dilatation of veins (Hobeika, Thompson et al. 2007, Lim and Davies 2009). The extracellular matrix homeostasis is regulated by a group of zinc-dependent endopeptidases called matrix metalloproteinases (MMPs) and their endogenous inhibitors, tissue inhibitors of metalloproteinases (TIMPs) (Somers and Knaapen 2006, Hobeika, Thompson et al. 2007). Of the 23 MMPs that have been identified in humans, at least 14 of them are expressed in vascular tissues (Lim, Shalhoub et al. 2010). Expression of various MMPs and TIMPs has been documented to varying degrees in varicose veins (Kockx, Knaapen et al. 1998, Kowalewski, Sobolewski et al. 2004), with expression in various layers of the vein wall (Gillespie, Patel et al. 2002, Kosugi, Urayama et al. 2003). Lim et al and others have noted MMP-TIMP imbalance in varicose veins (Badier-Commander, Verbeuren et al. 2000, Lim, Shalhoub et al. 2010). These finding suggest that MMPs may affect all layers of the venous wall, including the extracellular matrix structure, leading to wall degradation and varicose vein formation. However, over

expression of MMP-2 and MMP-9 has been shown to occur with increased magnitude and duration of venous wall tension. Furthermore, the MMP-2 induced by increased wall tension, caused significant venous relaxation (Raffetto, Ross et al. 2007, Raffetto, Qiao et al. 2008). These findings may suggest that the production of MMPs, which increases extracellular matrix degradation and venous relaxation, may in fact be secondary to blood stasis and venous hypertension.

MMPs have also been implicated in smooth muscle cell dysfunction. In a study of smooth muscle cells cultured from varicose veins, there was an imbalance of collagen production, with increased type I, but suppressed type III. The mechanism involved in this collagen degradation is likely linked to the expression of MMP-3. (Sansilvestri-Morel, Rupin et al. 2005). Other studies have found decreased apoptosis in smooth muscle cells from varicose veins. Apoptosis (programmed cell death, or internal suicide) in response to intrinsic or extrinsic signals, is important to maintain homeostasis of an organism. Abnormal apoptosis in smooth muscle cells may lead to disruption of normal tissue integrity and cause venous wall changes and dilatation in varicose vein pathogenesis (Ascher, Jacob et al. 2000, Ducasse, Giannakakis et al. 2005).

1.4. Classification

The CEAP (Clinical-aEtiology-Anatomy-Pathophysiology) classification was developed in 1994 by an international ad hoc committee of the American Venous Forum, and endorsed by the Society for Vascular Surgery. It was incorporated into the Reporting Standards in Venous Disease in 1995. The aim was to achieve uniformity in reports of management of venous diseases, as well as correctly diagnose, and systemically guide the daily clinical investigation, decision making and appropriate management of patients with venous disorders (Beebe, Bergan et al. 1996). The basic CEAP classification was refined in 2004 to include the division of C4 into 2 subclasses to reflect the severity of disease and risk for ulcer development; the introduction of a descriptor “n” for E, A, and P classification, where no venous abnormality is identified (Eklof, Rutherford et al. 2004). The CEAP classification is summarised below:

Clinical classification (C0-6)

C0 No visible or palpable signs of venous disease

C1 Telangiectasies or reticular veins

C2 Varicose veins

C3 Edema without skin changes

C4 Skin and subcutaneous tissue changes ascribed to venous disease

C4a Pigmentation or eczema

C4b Lipodermatosclerosis or atrophie blanche

C5 Skin changes as above, with healed ulceration

C6 Skin changes as above, with active ulceration

Each limb is further characterised as asymptomatic (A), or symptomatic (S). The higher clinical classes have more severe signs, and may also have features of a less severe class.

aEtiologic classification

Ec Congenital

Ep Primary

Es Secondary

En No venous cause identified

Venous dysfunction may be congenital (c), primary (p), or secondary. Congenital disorders are present at birth, but may not be diagnosed until later. Primary venous

dysfunction is of unknown cause (not congenital), while secondary dysfunction results from an acquired condition such as deep venous thrombosis.

Anatomic classification

As Superficial veins

Ap Perforator veins

Ad Deep veins

An No venous location identified

Multiple venous systems may be involved, in any combination.

Pathophysiologic classification

Pr Reflux

Po Obstruction

Pr,o Reflux and obstruction

Pn No venous pathophysiology identified

The severity of venous dysfunction is influenced by the anatomic location of any reflux or obstruction (Porter and Moneta 1995). The advanced CEAP therefore

includes the details of any of 18 anatomic segments, used for locators for venous pathology.

1.5. Clinical features

The clinical presentation of varicose veins varies among patients (Teruya and Ballard 2004). Patients may be asymptomatic apart from the appearance of the varicosities, but in general, patients fall into 2 groups with regards to clinical presentation: those without complications, and those with complications.

Patients without complications may report localised symptoms such as pain, burning or itching, or more generalised symptoms such as aching legs, leg swelling or fatigue, heaviness, tingling, or restless legs (Jones and Carek 2008). These symptoms which are due to venous hypertension tend to be worse at the end of the day, especially after prolonged standing, and usually are resolved by walking, or sitting with leg elevation (Jones and Carek 2008). Patients who develop complications may present with skin pigmentation, varicose eczema, superficial thrombophlebitis, venous ulceration, haemorrhage and lipodermtosclerosis (Jones and Carek 2008).

The relationship between symptoms and severity of venous reflux is inconsistent. Also, many of these symptoms may be present in people with no clinical evidence of varicose veins (Bradbury, Evans et al. 1999). In men, although the most common symptom was cramps, the Edinburgh vein study found only itching to be

significantly associated with trunk varices. Women were more likely to report a wide range of leg symptoms, and although showed significant association between symptoms and presence of trunk varices, the clinical significance of this is doubtful. Frequency of symptoms of both uncomplicated and complicated varicose veins increases linearly with age in both sexes (Bradbury, Evans et al. 1999, Chiesa, Marone et al. 2007).

Because varicose veins rarely cause acute life threatening complications, they have long been given low clinical priority, and regarded as a cosmetic nuisance (Campbell 2006). However, varicose veins have a significant impact on quality of life (QoL), and several studies have consistently shown that successful treatment of varicose veins is associated with significant QoL benefits (Smith, Garratt et al. 1999, Mekako, Hatfield et al. 2006, Carradice, Mekako et al. 2011).

1.6 Assessment and investigations

The assessment of patients with varicose veins is aimed at determining if the symptoms are due to venous disease, detect any complications, and detects other significant pathology. It has been estimated that up to a third of patients presenting with varicose veins, have symptoms unrelated to varicose veins, and may be worried about deterioration / complications (London and Nash 2000). The history attempts to elucidate previous DVT, leg fractures, previous venous surgery and a family history of varicose veins. Physical examination usually includes abdominal

examination to detect any scars, dilated collaterals, and any abdomino-pelvic cause of the varicosities.

Limb examination is important, and is performed with patient in the erect position. It aims to determine the distribution of the varicosities, in particular, whether they arise from the GSV or SSV. The examination also includes a record of any complications such as skin changes, lipodermatosclerosis and ulceration. The performance of clinical tests such as tourniquet (Perthes and Trendelenburg), tap, and cough tests to define the source of reflux, are usually inaccurate, only variably helpful, and have largely been replaced by the use of hand held continuous wave doppler (Campbell, Niblett et al. 1997, Kim, Richards et al. 2000).

Imaging studies are usually performed as part of the assessment of patients with varicose veins. Colour flow duplex ultrasound scan has largely replaced phlebography as the gold standard imaging modality for venous disease (Neglen and Raju 1992, Baker, Burnand et al. 1993, Cavezzi, Labropoulos et al. 2007). The use of duplex scanning should prevent inappropriate and / or incomplete operation (Mercer, Scott et al. 1998, Wills, Moylan et al. 1998), although another study by Kent and Weston (Kent and Weston 1998) showed that detailed clinical evaluation using hand held doppler resulted in appropriate surgery in 94% of patients with primary varicose veins. With limited resources and pressures on vascular laboratories and radiology units, duplex scanning is indicated in recurrent varicose

veins, suspected SSV incompetence, presence of complications, and in patients with history of DVT (Wolf and Brittenden 2001). This policy is however changing, as many vascular surgeons now routinely scan their patients in clinic, obviating the need for more formal “departmental scans”. Duplex scan is useful for mapping reflux within the saphenous systems, detecting SSV disease, locating SPJ and incompetent non-junctional perforators, as well as evaluating the deep venous system. In this era of increasing use of endovascular technologies for the treatment of varicose veins, it is becoming almost routine for vascular surgeons to perform duplex scanning (Bachoo 2009). Blomgren et al showed that the use of preoperative duplex scan resulted in changes to the planned surgery, and more importantly, resulted in less residual and recurrent varices at 2 years (Blomgren, Johansson et al. 2005). Magnetic resonance venography is not routinely used in varicose veins, but remains the most sensitive and specific non invasive test for anatomic obstruction (Koizumi, Horie et al. 2007).

Other investigations such as varicography (venography) and plethysmography have largely been replaced by duplex ultrasound scan, and rarely used in day to day usual clinical practice (Gloviczki, Comerota et al. 2011).

1.7. Treatment of varicose veins and post intervention outcomes

The optimum management of varicose veins requires accurate identification of the source of venous incompetence (Beale and Gough 2005). It is important to realize

that not all patients need to be treated, and for some patients with uncomplicated varicose veins, reassurance and explanation is all that is required (London and Nash 2000). When it is decided to treat a patient, the most appropriate treatment for each patient has to be decided. This decision is based on the patient's symptoms, pattern and extent of reflux, presence of co-morbidities / fitness of patient, patient expectations, and of course skill of the surgeon and availability of treatment modalities. A brief overview of treatment options and summary of evidence for them is presented below.

Compression hosiery

The use of compression stockings can relieve symptoms, improve venous haemodynamics, and prevent deterioration of skin changes associated with venous hypertension (Ibegbuna, Delis et al. 1997, Zajkowski, Proctor et al. 2002). Compression acts by providing graduated radial pressure between the ankle and the knee or thigh. The maximal pressure is exerted at the ankle, and reduces to 75% at the calf, and 50% at the thigh (Sam and Bradbury 2007). The compression combined with the action of the calf muscle pump facilitates cephalad blood flow and venous return (Somerville, Brow et al. 1974). Compression is usually most effective at an ankle pressure of 20 - 30 mmHg (class 2), (Hirai, Iwata et al. 2002),

but class 1 (15 - 20 mmHg) and class 3 (30 - 40 mmHg) compression are also utilised. The effect of compression is limited to the period during which it is worn, and the tolerance and compliance by patients is variable (Beale and Gough 2005). Compression is often used as first line treatment in the community, and can be used as primary treatment for some patients who are otherwise not candidates for any interventional therapy. Compression is also used as an adjunct to invasive management, for variable lengths of time. The ESCHAR trial showed good evidence for the efficacy of compression after varicose vein surgery in the reduction of ulcer recurrence (Gohel, Barwell et al. 2007). The efficacy of compression stockings for primary management of varicose veins is limited. In the REACTIV trial for example, Michaels and colleagues found that over half of their patients randomised to conservative management of their varicose veins with compression, expressed unhappiness with their treatment, and crossed over to have surgery (Michaels, Campbell et al. 2006). Again, Anderson et al found no significant difference between placebo plus stockings versus placebo alone, in terms of scores for symptoms of pain, heaviness, itching, swelling, night cramps and cosmetic appearance, although the study may have lacked power to detect clinically significant changes (Anderson, Geraghty et al. 1990). There are however, reports of marked improvement in pain, swelling, skin pigmentation, activity and wellbeing, after the use of compression at 30 to 40mmHg in compliant patients (Motykie, Caprini et al. 1999).

There are no reported complications associated with the appropriate use of compression hosiery, apart from reported difficulty with getting them on, cost, etc, which may affect compliance (Beale and Gough 2005). Skin breakdown and frank necrosis have been reported after incorrectly measured or applied compression garments (Callam, Ruckley et al. 1987).

Sclerotherapy

Sclerotherapy, which involves the injection of a sclerosant into a vein, was made popular by the work of Henry and Fegan in the early 1970s (Henry, Fegan et al. 1971). Sclerotherapy works by causing a chemical thrombophlebitis, occlusion and eventual fibrosis (Kern 2002). Three categories of sclerosants are in use: detergent solutions (sodium tetradecyl sulphate [STD] and polidocanol), osmotic solutions (eg hypertonic saline), and chemical irritants / corrosive agents (eg glycerine). Polidocanol is popular in Germany and many European countries, whereas in the UK, France and USA, STD is more widely used (Stucker, Kobus et al. 2010). Some of the documented variables which may affect the efficacy of sclerotherapy include: type of sclerosant (but, RCT showed no significant difference between STD and polidocanol; (Goldman 2002); physical state (foam or liquid) of sclerosant used (foam more effective than liquid; (Ouvry, Allaert et al. 2008, Rabe, Otto et al. 2008); and concentration of sclerosant used (higher concentration more effective; (Ceulen, Bullens-Goessens et al. 2007).

Sclerotherapy is more effective than conservative therapy or compression alone in reducing aching and improving cosmesis, but not for heaviness and itching and swelling (Michaels, Campbell et al. 2006, Tisi 2007). Old studies (Rutgers and Kitslaar 1994, Dwerryhouse, Davies et al. 1999) have shown superiority of conventional surgery over sclerotherapy in terms of venous and clinical reflux. The ongoing recently commissioned, nationwide Comparision of LAser Surgery and foam Sclerotherpy (CLASS) Trial should hopefully answer the question of camparison of these modalities for the management of primary varicose veins. A recently published trial by Rasmussen et al, akin to the CLASS trial, randomised 500 patients to receiving one of EVLA, radiofrequency ablation, foam sclerotherapy, and surgery. At 1 year, significantly more GSVs were refluxing in the foam sclerotherapy group than in any other group (Rasmussen, Lawaetz et al. 2011). At present, outside of the CLASS and other trials, sclerotherapy is most often used as an adjunct to other modes of management of varicose veins (Tisi 2007).

Complications and adverse events following sclerotherapy can be grouped as neurosensorial deficits (visual disturbances, headaches, migraines, Transient Ischaemic attacks and strokes), thrombotic complications (DVTs, superficial thrombophlebitis, PEs), general complications (allergy, anaphylaxis, infection, chest tightness), and local complications (hyper pigmentation, intra arterial / extra-

venous injection, skin ulceration and necrosis, nerve injury). These complications occur with variable frequency depending on a number of factors including technical skills, type, nature, concentration, and volume of sclerosant used; overall however, they are estimated to occur at a rate of 0.22% per session with liquid, and 0.58% per session with foam (Guex, Allaert et al. 2005).

Endovascular therapies

In recent years there has been an endovascular revolution, resulting in the emergence of minimally invasive options for the management of varicose veins. The main front runners in this revolution are endovenous laser ablation (EVLA) and radiofrequency ablation (Stirling and Shortell 2006, Carradice, Mekako et al. 2011). Vein ablation is achieved by different technologies, but the principle and mechanism of action is similar, in the fact that thermal damage is done to the vein wall, with subsequent sclerosis and disappearance of the vein, as healing and re-absorption take place (Bachoo 2009). This current work did not use radiofrequency ablation; therefore the focus will be on endovenous laser ablation, although a brief overview is given of radiofrequency ablation.

Endovenous delivery of laser energy was first reported in 1999 (Bone 1999), and endovenous laser ablation of the GSV achieved 2 years later (Navarro, Min et al. 2001). One major advantage of EVLA is that it is performed under local

anaesthesia, as an outpatient procedure. The details of the procedure will be given later in the methodology section, but in brief, a laser fibre is inserted under ultrasound guidance into the GSV or SSV and advanced to the SFJ / SPJ. Perivenous tumescent local anaesthetic is then infiltrated along the length of the vein to be ablated. Tumescent anaesthetic fluid provides pain relief, acts as a heat sink to absorb heat and protect surrounding tissues, as well as increase vein wall contact with the laser fibre, by compression (Min and Khilnani 2005, van den Bos, Kockaert et al. 2008). The laser fibre is then withdrawn at a speed of 1 – 3 mm per second, as it is fired. Compression bandaging is then applied for variable periods. At the time this work was done, EVLA was a staged procedure, with initial ablation followed in 6 – 12 weeks by outpatient sclerotherapy in up to 90% of cases (Beale and Gough 2005).

The exact mechanism by which EVLA causes damage to the vein wall is still unclear, though various mechanisms have been proposed. Heat damage to the vein wall, either directly from the hot laser fibre tip (reaching temperatures of between 800 and 1300 degrees Celcius), or the effect of boiling blood bubbles, which transfer heat from the fibre tip to the vein walls, where they condense and dissipate the heat energy, appear to be the most likely mechanisms (van den Bos, Kockaert et al. 2008, van den Bos, Kockaert et al. 2009).

Various laser modalities and energy deliveries have been used, but 810 nm diode delivering power at 10 – 14 Watts has been most widely used (Beale and Gough 2005). A recent study by Vuylseteke et al compared 1500nm and 980nm diode laser in EVLA of GSV varicosities. They found similar occlusion rates, but the higher wavelength delivery was associated with less post procedure induration (Vuylsteke, De Bo et al. 2011). Other studies have shown similar findings of equivalent efficacy, but less adverse effects with the longer wavelengths laser light (Proebstle, Moehler et al. 2005, Kabnick 2006). The clinical and QoL efficacy of EVLA has been demonstrated by several studies, with reported immediate and short-term GSV closure rates of 94% - 100%, and at least 90% after 3 years (Beale and Gough 2005, Min and Khilnani 2005, Carradice, Mekako et al. 2011). Both generic and disease specific QoL are significantly improved by EVLA of truncal varicosities in the short and medium term (Rasmussen, Bjoern et al. 2010, Carradice, Mekako et al. 2011).

Reported complications following EVLA include bruising, thrombophlebitis, hyper pigmentation, skin burns, paraesthesia and DVT (Mundy, Merlin et al. 2005, Mekako and Chetter 2007).

Radiofrequency ablation (RFA) was introduced in 1999 with early reports appearing in 2000 (Gloviczki, Comerota et al. 2011). The procedure is similar to EVLA, in respect of ultrasound guided introduction of catheter into the varicose

vein, use of tumescent anaesthetic and catheter withdrawal during treatment. RFA however utilises a different modality for endovenous thermal delivery. The introduction of the ClosureFast® catheter which has a 7cm area of heating in the probe, improved the speed of treatment delivery, and the efficacy of RFA (Health Quality 2011). Complications and efficacy are similar to EVLA, especially with the 2nd generation catheters, although there may be less bruising and possibly higher rates of DVT with RFA as compared with EVLA (Gloviczki, Comerota et al. 2011, Health Quality 2011).

Surgery

Standard surgery for varicose veins dates back over a century, when Babcock described a 'new procedure for the extirpation of varicose veins of the leg' (Babcock 1907). Surgery has since been regarded as the gold standard for treatment of varicose veins, and the yard-stick against which more recent treatment forms are compared. Surgery for varicose veins is one of the most common interventions performed in the UK and most of the Western World (Department of Health 2005).

Various surgical techniques and options have been described and utilized in the management of both primary and recurrent varicose veins. For varicosities of the GSV, which are by far the most common, the evidence based surgical

recommendation is for patients to undergo a high tie (sapheno-femoral junction ligation), with stripping of the GSV to about one hand's breadth below the knee, and phlebectomies (multiple stab avulsions) of tributary varicosities (Beale and Gough 2005). Surgery is usually performed as a day-case procedure, under a general anaesthetic. The detailed surgical procedure will be described later in the methods section, but briefly, it entails making a groin-crease incision, identifying the SFJ and ligating this, after ligation and division of the main tributaries of the GSV at or close to the SFJ. These tributaries should be ligated and divided beyond their secondary branch points to reduce the risk of reconnection and subsequent recurrence. The GSV is then stripped, preferably using a PIN (perforator invagination) stripper, which causes inversion of the vein as it is being stripped. Inversion stripping is believed to reduce bleeding and minimize the chances of nerve damage, although this was not proved by previous RCTs (Durkin, Turton et al. 1999, Lacroix, Nevelsteen et al. 1999). Tributary varicosities are then avulsed through multiple stab incisions, using vein hooks or kocherised mosquito forceps. Post operatively, compression is applied by bandaging or stockings for a variable length of time.

Various modifications of the above procedure have been (and still being) used in an attempt to deal with the GSV, improve results, and reduce complications. These include: the use of tourniquet to reduce blood loss (Sykes, Brookes et al. 2000);

cryostripping, which has similar clinical and QoL outcomes as standard stripping, but causes less bruising (Menyhei, Gyevnar et al. 2008); transilluminated powered phlebectomy, which requires less incisions for phlebectomies, but associated with significantly more bruising, prolonged pain and poor early postoperative QoL as compared with hook avulsions (Chetter, Mylankal et al. 2006). Sapheno-femoral junction ligation has also been combined with foam sclerotherapy or EVLA of the GSV. Other surgical procedures such as ambulatory conservative haemodynamic management (CHIVA), perforator surgery, and external valvular cuffs / stents exist, but are not described in this work.

Complications associated with varicose vein surgery include bleeding (which may include major injuries to the femoral vessels), haematoma and wound complications including infection can occur in up to 10% of cases (Corder, Schache et al. 1991, Mekako, Chetter et al. 2010), nerve injuries, which may range from paraesthesia, to foot drop, and venous thrombo embolism. Recurrence rates after surgery vary depending on definition, initial procedure performed, mode of identification, and length of follow up (Beale and Gough 2005). Quoted rates of recurrence range from 7% - 70% (Winterborn, Foy et al. 2004), although following surgery with GSV stripping, the rates of clinical recurrence are between 25% and 37% (Munn, Morton et al. 1981, Dwerryhouse, Davies et al. 1999). Overall, about 20% of varicose vein surgeries are performed for recurrent disease (Bradbury,

Stonebridge et al. 1993). It would be anticipated that in the era of endovenous therapies, this proportion would reduce.

Surgery has been shown to be effective in relieving symptoms, and improving QoL (Mackenzie, Lee et al. 2002, MacKenzie, Paisley et al. 2002, Carradice, Mekako et al. 2011). Wound infection following varicose vein surgery can be a significant limitation to the delivery of effective surgical intervention. Surgical site infections and the use of prophylactic antibiotics in varicose vein surgery are now explored further.

Surgical site infections (SSIs) and use of antibiotic prophylaxis in varicose vein surgery

The rate of groin wound infection following varicose vein surgery may reach 16% (Corder, Schache et al. 1991, Hayden and Holdsworth 2001, Hirsemann, Sohr et al. 2005). SSIs are the commonest of hospital acquired infections among surgical patients in the UK, affecting up to 10% of patients. In the USA, this proportion reaches up to 38% (Mangram AJ, Horan TC et al. 1999, Nosocmial Infection National Surveillance Service 2001). When patients develop an SSI following varicose vein surgery, it is usually a superficial incisional infection, the characteristics of which must meet the following Centres for Disease Control and Prevention (CDC) definition criteria (Horan, Andrus et al. 2008):

Infection occurs within 30 days after the operative procedure and involves only skin and subcutaneous tissue of the incision, and patient has at least 1 of the following:

Purulent drainage from the superficial incision

Organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision

At least 1 of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat, and superficial incision is deliberately opened by surgeon and is culture positive or not cultured. A culture-negative finding does not meet this criterion.

Diagnosis of superficial incisional SSI by the surgeon or attending physician.

The CDC definition is only one of several definitions for wound infection used in published studies. There are several other definitions for identification and surveillance of SSIs, including scoring systems like the ASEPSIS method, which was designed for use in clinical trials of antibiotic prophylaxis (Wilson, Treasure et al. 1986). The ASEPSIS method was used in this study and more details will be given in the methods section.

SSIs are a significant problem which limits the potential benefits of surgical interventions. The impact on hospital costs and postoperative length of stay is considerable.

The use of antibiotics to prevent SSIs has long been established (Mangram, Horan et al. 1999). In vascular surgery, although antibiotics have been shown to be effective in preventing SSI in arterial bypass surgery (Turtiainen, Saimanen et al. 2010), no similar studies have previously looked specifically at their use in varicose vein surgery.

What outcomes are important in the treatment of varicose veins?

The aim of any form of intervention in patient care whenever possible is to eradicate the problem / control the symptoms and preserve or restore quality of life, with minimal complications (Tisi 2007). Outcome assessment of therapy for varicose veins includes standardised objective criteria that reflect patient symptoms, characteristic signs, and objective measures of functional and disease specific quality of life (Gloviczki, Comerota et al. 2011). Varicose veins cause cosmetic concerns, symptoms and complications, and also affect quality of life. The optimal management of varicose veins must therefore address these problems and take patient expectations into account. In a study investigating patient preferences and expectations in varicose vein treatment, Shepherd et al

(Shepherd, Gohel et al. 2010) found that although only half of 111 patients knew of endovascular ablative therapies, the majority of patients would prefer a local anaesthetic procedure for their varicose vein treatment. The majority of their patients (80%) would however be influenced in their choice of treatment, by their surgeon. This would indicate that to a large extent, the surgeon is in the driving seat with regards to optimal management for each patient. On the basis of current evidence, it would appear that the minimally invasive therapies especially EVLA offer an ideal management for varicose veins, with excellent efficacy, minimal side effects / complications, and preservation of quality of life. Not all varicose veins are however suitable for these minimally invasive therapies and a significant proportion of patients who undergo EVLA would require subsequent adjunctive procedures. It therefore means that surgery remains an important option for management. Surgery, as has been previously highlighted, although very effective, has significant complications, especially wound complications.

It would therefore be likely that the optimal treatment for varicose veins is not a one cap fits all modality, and that several factors are taken into reckoning. Since it is the objective of intervention to eradicate varicose veins, eliminate symptoms, and preserve quality of life, the “ideal” mode of therapy may well be patient and varicosity specific, and involve a combination of techniques.

2. AIMS

Since the introduction of varicose vein surgery by Babcock over a century ago, treatment of varicose veins has undergone modification and modernisation with the objective of improving efficacy and minimising complications. Analysis of quality of life outcomes has now become common place in assessing the impact of interventions. Indeed this is now recommended in analysis of outcomes of intervention for varicose veins (van Korlaar, Vossen et al. 2003). In the last decade, the minimally invasive therapies have undergone a revolution, with expansion of indications and applicability. There is therefore the need to explore the available treatment options with the aim of optimising the management of varicose veins.

Important questions to address in the optimal management of varicose veins would include:

What proportion of patients with varicose veins can undergo EVLA?

How can EVLA be optimised for efficacy, reduce the need for subsequent procedure, and yet preserve the excellent patient experience?

How does EVLA compare with surgery?

Can the use of prophylactic antibiotics reduce wound complications following surgery for varicose veins?

These and other issues are the focus of this present work. This work does not focus on the use of foam sclerotherapy or other forms of endovenous therapies besides laser ablation.

3. METHODS

To address the various issues to be dealt with in this present work, 4 studies were performed:

Study 1

What proportion of patients with varicose veins is suitable for endovenous laser ablation?

Study 2

Combined endovenous therapy and ambulatory phlebectomy: refinement of a new technique *(Eur J Vasc Endovasc Surg 2006; 32(6); 725 - 729)*

Study 3

A non randomized controlled trial of endovenous laser therapy and surgery in the treatment of varicose veins *(Ann Vasc Surg 2006; 20(4): 451 - 457)*

Study 4

Randomized clinical trial of co-amoxiclav versus no antibiotic prophylaxis in varicose vein surgery *(Br J Surg 2010; 97(1): 29 - 36)*

3.1. STUDY 1

AN ANALYSIS OF THE SUITABILITY FOR ENDOVENOUS ABLATION IN PATIENTS WITH LOWER LIMB VARICOSE VEINS

The introduction of minimally invasive treatment for varicose veins brought the appeal of combining efficacy with minimal negative impact on QoL. As with any new technology, there was caution mixed with optimism and guarded indications. In the first year of introduction of EVLA in our centre, we aimed to see what proportion of patients with varicose veins could undergo laser ablation of their varicosities.

Study Design

This study was designed as a prospective observational series

Recruitment

Over a 12 month period beginning June 2004, a random selection of patients on a waiting list for varicose vein surgery was invited to attend for a duplex scan to assess their suitability for endovenous ablation.

All patients listed for unilateral primary SFJ ligation (high tie), stripping of the great saphenous vein, and multiple stab avulsions (phlebectomies) were identified. This formed the primary inclusion criterion. A random sample of these patients was then generated, and the selected patients were invited to attend the vascular laboratory for duplex ultrasound scan. Suitability criteria for laser ablation were devised, using the best available evidence on EVLA in the then current literature. These criteria were suggested in order to limit the incidence of technical and clinical failure of the procedure.

Suitability Criteria

The following suitability criteria were employed:

Isolated SFJ incompetence and/or GSV reflux

Absence of incompetent major antero-lateral (anterior accessory GSV) thigh branch terminating within 2cm of the SFJ

Absence of duplicated GSV

Perigenicular GSV diameters greater than 5mm

Patient acceptance of local anaesthetic procedure

Duplex scanning

Scanning was performed using a SonoSite Titan® machine (SonoSite Inc. Bothell, WA) with a 5 –10 MHz 38mm broadband linear array probe. All limbs were scanned in the upright position, with the limb externally rotated, and the weight taken on the contra lateral limb. The superficial and deep veins, including junctions and perforators were examined. Duplex scanning was carried out in B and colour Doppler modes. Antegrade and retrograde flow was examined by a distal compression-release technique, augmented with the valsalva manoeuvre. Reflux was regarded as a retrograde flow of >0.5 seconds on pulsed-wave Doppler, as previously defined for superficial veins of the lower limb (Labropoulos, Tiongson et al. 2003). All scans were performed by a vascular ultrasound scientist and corroborated by a vascular surgeon trained in vascular ultrasound. Data was entered prospectively into a specially designed database.

3.2. STUDY 2

AN ANALYSIS OF THE FEASIBILITY AND ACCEPTABILITY OF EVLA AND AMBULATORY PHLEBECTOMY IN PATIENTS WITH LOWER LIMB VARICOSE VEINS

EVLA is effective in eradicating reflux in the treated vein. It is generally performed under local tumescent anaesthesia and is associated with very good patient tolerability, acceptance and satisfaction. As treatment was traditionally limited to the truncal vein, 30% - 99% of patients required secondary treatment of residual varicosities, usually in the form of compression sclerotherapy (Beale, Mavor et al. 2004). The need for subsequent secondary therapy means patients often require repeated visits to the treatment centre, as well as face associated potential complications of sclerotherapy; this may be a relative limitation to the otherwise high patient acceptability of endovenous laser therapy.

This study aimed to assess if combining EVLT and ambulatory phlebectomy as a single procedure (a combination procedure were have called EVLTAP), was feasible, effective and acceptable to patients.

Study Design

This study was designed as a prospective observational series

Recruitment

Patients were selected by screening the day-case varicose veins waiting list, and inviting patients listed for high tie, GSV stripping and avulsions for duplex scan (see details in study 1). Patients, who matched the local suitability criteria as previously detailed, were offered EVLTAP. Patients with short saphenous varicosities, anterolateral thigh branch incompetence, previous varicose vein surgery and GSV with a diameter of less than 5mm at the knee were excluded.

All patients signed an informed consent form before undergoing EVLTAP. The study was approved by the Hull and East Riding Local Research Ethics Committee and carried out in accordance with the Helsinki Declaration.

Technique Description

All procedures commenced with laser ablation of the incompetent GSV. The SFJ was identified by duplex ultrasound scan (DUS) in the upright position and the course of the GSV followed down to the knee, with intermittent skin markings. The patient was positioned in the reverse trendelenburg position and skin preparation and draping carried out. The peri-genicular entry point into the GSV was again identified and 1-2 ml of 1% plain lignocaine infiltrated into the skin. Percutaneous entry into the GSV was gained, using a 19-guage needle under ultrasound guidance. In 2 patients where percutaneous cannulation of the GSV at the knee

was impossible due to small vein size (following vein wall spasm), open cannulation was achieved via a stab wound, and “hooking up” the vein. A 0.035-inch diameter J guide wire was inserted through the needle, which was subsequently removed. A 5F catheter was introduced over the guide wire and positioned within the GSV, immediately distal to the SFJ. Its position was confirmed by ultrasound, and the aspiration of non-pulsatile blood. A sterile bare-tipped laser fibre, 600μm in diameter was introduced into the catheter to its first mark (which placed its tip flush with the end of the catheter). The catheter was then withdrawn to the second mark on the fibre, while keeping the position of the laser fibre fixed. This resulted in protrusion of 2 cm of the bare-tipped laser fibre beyond the catheter tip. The fibre was locked in the catheter in this position. The patient was then positioned in Trendelenburg position to aid vein emptying.

Tumescent local anaesthetic solution was infiltrated along the whole length of the GSV to be ablated, using a 0.9mm X 180mm needle under ultrasound guidance. Tumescent anaesthetic solution was prepared by diluting 30ml of 2% lignocaine (with 1:200,000 adrenaline), in 500ml of saline). Tumescent local anaesthetic was also infiltrated around branch varicosities. Total local anaesthetic used in each case, did not exceed recommended maximum safe dose of 7mg/kg per patient.

Laser energy was delivered endovenously using an 810 nm diode laser generator (Diomed Ltd, Cambridge, United Kingdom). 12 or 14 W power in pulsed or

continuous mode was utilised. During the laser ablation process, manual compression was applied to the limb over the tip of the laser fibre to aid vein wall apposition and improve heat conduction.

Following laser ablation of the GSV from groin to knee, stab incisions of 1- 2 mm were made over varicosities, which were then avulsed using kocherised mosquito artery forceps or Mueller hooks as conventionally done. Steri-strips and gauze dressings were applied to stab wounds.

Panelast® (Lohmann & Rauscher International GmbH & Co. KG) elastic adhesive bandage was applied to the whole length of the treated limb post procedure and left in place until the first follow up at 1 week, when it was changed to a class II (30-40mmHg) full-length graduated support stocking that was worn for a further 5 weeks, except during sleep and baths. All patients were asked to walk immediately after the procedure, and to return to normal activities as soon as they felt comfortable. A 1-week course of non-steroidal anti-inflammatory drugs was prescribed for all patients with no contraindication to their use.

Postoperative Assessments and Outcome Measures

Pain

Pain was assessed on days 1, 4 and 7 using a visual analogue scale (VAS) rating of 0cm (no pain) to 10cm (worst imaginable pain). This was entered by patients in

a diary given to them at the completion of the procedure. Diaries were reviewed at 1-week follow up.

GSV occlusion rates on Duplex Ultrasound Scan

Duplex ultrasound scan was performed at 1 and 12 weeks post procedure to assess SFJ and GSV occlusion. Reflux was defined as greater than 0.5 seconds retrograde flow. All scans were performed by the same investigator to avoid inter observer variability

Subsequent interventions

Patients were assessed at 6 weeks, and any one who had residual varicosities was offered either sclerotherapy or further phlebectomies.

Patient Satisfaction

Patient satisfaction was assessed at 12 weeks using a VAS rating of 0cm (completely dissatisfied) to 10cm (completely satisfied). Patient satisfaction with cosmetic outcome and with overall treatment was assessed separately. The overall treatment satisfaction was a composite assessment that included treatment deliveries, length of procedure, follow up treatment and recovery. It gave an indication of patient acceptability of the procedure.

3.3. STUDY 3

A NON RANDOMISED CONTROLLED TRIAL OF ENDOVENOUS AND SURGICAL TREATMENT OF PATIENTS WITH VARICOSE VEINS

Surgery has been the gold standard for the treatment of varicose veins. Surgical treatment is effective at abolishing reflux, correcting symptoms and restoring quality of life (QoL) (Carradice, Mekako et al. 2011). More recently, minimally invasive therapies have emerged, which combine efficacy with diminished complication rates and high levels of acceptance. EVLA is one of the front runners in this endovascular revolution. It is a local anaesthetic procedure that can be performed on an ambulant basis, often as an office procedure. The procedure has impressive GSV ablation rates at up to 5 years follow up (Min and Khilnani 2005). Successful treatment should however not be interpreted only in the context of ablation rates, but also in respect of total patient well-being. Health related QoL is the patient-perceived functional effect of an illness and its consequent therapy. It has been proposed that QoL measures should be standard in studies involving patients with venous diseases (van Korlaar, Vossen et al. 2003).

The aim of this study was to compare early quality of life outcomes following surgery and EVLA in the treatment of patients with varicose veins.

Study Design

This trial was designed as a prospective, non-randomized, controlled observational study of patients undergoing endovenous and surgical treatment for lower limb varicose veins. We designed this study to function as a pilot study, the results of which would be utilized in a power calculation for a future randomized controlled trial with QoL measures as primary outcome.

Two groups of patients undergoing treatment for unilateral symptomatic varicose veins attributable to isolated SFJ incompetence and GSV reflux on preoperative duplex ultrasound scan were studied.

Patient Selection

Immediately prior to commencement of EVLA at our institution, consecutive consenting patients undergoing surgery for varicose veins were recruited into the surgery group. When EVLA commenced, all suitable consenting patients were recruited into the EVLA group.

Surgery Group

Patients in the surgery group underwent conventional SFJ ligation, stripping of the GSV to knee level, and multiple stab phlebectomies under general anaesthesia. All

procedures were carried out in the day surgery unit and performed by a consultant vascular surgeon or competent Specialist Registrar. Crepe bandage compression was applied post op for 2 - 4 hours, after which it was changed to a class II (20 - 40 mmHg) full-length graduated support stocking as patient was discharged. This was worn continuously for 1 week and then during the day for a further 4 weeks. All patients were encouraged to walk as much as possible and to return to normal activities as soon as they felt able. All patients without contraindications were prescribed a 1-week course of non steroidal anti-inflammatory tablets (Diclofenac 50mg to be taken 3 times daily).

EVLA group

These patients underwent EVLA with concomitant multiple stab phlebectomies under tumescent local anaesthetic. All procedures were carried out by a single vascular surgeon proficient in EVLA technique, and took place in the surgical out patient clinic minor theatre. The SFJ was identified by duplex ultrasound scan in the upright position and the course of the GSV followed down to the knee, with intermittent skin markings. The patient was then positioned in the reverse Trendelenburg position and skin preparation and draping carried out. The peri-genicular entry point into the GSV was again identified and 1-2 ml of 1% plain lignocaine infiltrated into the skin. Percutaneous entry into the GSV was gained, using a 19-guage needle under ultrasound guidance. A 0.035-inch diameter J

guide wire was inserted through the needle, which was subsequently removed. A 5Fg catheter was introduced over the guide wire and correctly positioned within the GSV, immediately distal to the SFJ. Its position was confirmed by ultrasound. A sterile bare-tipped 600μm laser fibre was introduced into the catheter to its first mark, placing its tip flush with the end of the catheter. The catheter was then withdrawn to the second mark on the fibre, while keeping the position of the laser fibre fixed. This resulted in protrusion of 2 cm of the bare-tipped laser fibre beyond the catheter. The fibre was locked within the catheter in this position. The patient was positioned in Trendelenburg position to aid vein emptying.

Perivenous tumescent local anaesthetic (0.2% lignocaine with 1:200,000 adrenaline) was infiltrated along the whole length of the GSV to be ablated, using a 0.9mm x 180mm needle under ultrasound guidance. Local anaesthetic was also infiltrated around branch varicosities in a field block fashion. Total local anaesthetic did not exceed recommended maximum safe dose per patient.

Laser energy was delivered endovenously using an 810 nm diode laser generator (Diomed Ltd, Cambridge, United Kingdom). 12 or 14 W power in pulsed or continuous mode was utilized. During the ablation process, manual compression was applied to limb, over the tip of the laser fibre to aid vein wall apposition and improve heat conduction to vein wall. Following laser ablation of the GSV from groin to knee, stab incisions of 1- 2 mm were made over varicose tributaries, and

the veins avulsed using mosquito artery forceps or Mueller hook as conventionally done. Steri-strips and gauze dressings were applied to stab wounds.

Panelast® (Lohmann & Rauscher International GmbH & Co. KG) elastic adhesive bandage was applied to the whole length of the treated limb post procedure and left in place till the first follow up at 1 week, when it was changed to a class II (20-40mmHg) full-length graduated support stocking that was worn for a further 5 weeks, except during sleep and baths. All patients were asked to walk immediately after the procedure, and to return to normal activities as soon as they felt comfortable. Post operative analgesic / anti-inflammatory regime was as in the surgery group.

Success of EVLA was confirmed by duplex ultrasound scanning at 1 week and 12 weeks.

Postoperative Assessments and outcome measures

Patients were assessed prior to intervention, and at 1 week, 6 weeks and 12 weeks post procedure, using the medical outcomes short form 36 (SF-36) health survey, Aberdeen varicose veins questionnaire (AVVQ), and the venous clinical severity score (VCSS).

The *SF-36* is a widely used generic QoL instrument that has been demonstrated to be valid, reliable and sensitive (Baker, Turnbull et al. 1995). It consists of 36

individual items aggregated to form 8 domains: Physical Functioning (PF), Role-Physical (RP), Bodily Pain (BP), General Health (GH), Vitality (VT), Social Functioning (SF), Role Emotional (RE) and Mental Health (MH). Each domain is scored from 0 (worst score) to 100 (best score). The 8 domains (or scales) are aggregated to form two distinct component summary measures – Physical and Mental component summary measures. Three scales (PF, RP, BP) correlate most highly with the physical component and contribute most to the scoring of the Physical Component Summary (PCS) measure. The mental component correlates most highly with the MH, RE, and SF scales, which also contribute most to the scoring of the Mental Component Summary (MCS) measure. Three of the scales (VT, GH, and SF) have significant correlations with both components (Ware, Kosinski et al. 1994). As a general QoL measurement tool, the SF-36 may be used to compare health status both among patients with the same condition and between patients with different conditions. It may also be administered to general populations to see how a particular condition causes deviation from normal population standards (Ruta, Abdalla et al. 1994).

The *AVVQ* is a validated disease – specific health related QoL instrument for lower limb venous disease (Garratt, Macdonald et al. 1993). The questionnaire has 13 questions which cover all aspects of varicose vein clinical presentation including distribution, symptomatology, complications and management (analgesia and

compression). It was designed in 1993, with two independent vascular surgeons assigning weights to the individual questions, in proportion to the perceived contribution to severity of the disease (or the intervention) of that particular question. (Garratt, Macdonald et al. 1993). It gives a single disease-specific index scored from 0 (no venous symptoms) to 100 (extreme venous symptoms). As a disease – specific instrument, the Aberdeen Questionnaire, is believed to be more responsive to clinically important changes in health as a result of an intervention than generic instruments. The *VCSS,* introduced by Rutherford and colleagues in 2000, is the American Venous Forum's modification of the clinical score of the Clinical-Etiologic-Anatomic-Pathophysiologic (CEAP) classification of chronic venous disease. It was designed to be a quantifiable measure of disease severity, dynamic enough to measure change in response to treatment (Rutherford, Padberg et al. 2000). It scores 9 clinical characteristics of chronic venous disease in varying grades of severity, and has been validated for severity scoring in varicose vein surgery (Kakkos, Rivera et al. 2003). It correlates well the CEAP score, as well as with ultrasound assessment of the severity of venous incompetence or obstruction (Gloviczki, Comerota et al. 2011). VCSS assessment was performed prior to, and at 12 weeks post treatment.

Statistical analysis

Data was collected prospectively, and entered into a specifically designed database. Statistical analysis was performed with SPSS for Windows version 12 (SPSS Inc, Chicago Ill). Mann-Whitney test was used for intergroup analysis. Intragroup analysis was performed using Friedman test (across all time points) and Wilcoxon ranked sum test (used for comparing 2 time points). Adjustment for baseline differences between the groups was done by an analysis of co-variance (ANCOVA). Results are expressed as median (interquartile range [IQR]), and $p < 0.01$ was considered statistically significant.

Ethics

This study was approved by the Hull and East Riding Local Research Ethics Committee and by the Research and Development Unit of the Hull and East Yorkshire (NHS) Trust.

3.4. STUDY 4

A RANDOMISED CONTROLLED TRIAL OF PROPHYLACTIC ANTIBIOTICS IN PATIENTS UNDERGOING SURGICAL TREATMENT OF VARICOSE VEINS

Varicose vein surgery is clean surgery, and therefore has associated predicted wound infection rates of 1% - 5% (Garner, Jarvis et al. 1988). There is however, considerable variability in reported wound infection rates, ranging from 1.5% - 16% (Corder, Schache et al. 1991, Hayden and Holdsworth 2001, Hirsemann, Sohr et al. 2005). The true value of prophylactic antibiotics in clean non-implant surgery is unresolved, and at the time of this study, there was no level-1 evidence specifically examining the value of prophylactic antibiotics in varicose vein surgery. This study aimed to assess postoperative groin wound complications following surgery for varicose veins, and examined the use of prophylactic antibiotics in this situation.

Study Design

This study was designed as a double blind randomized controlled trial, to study the effect of a single-dose prophylactic antibiotic on wound-related complications following varicose vein surgery. Two parallel groups were compared. The

intervention group received co amoxiclav, while the control group received no medication.

Study Population and Setting

The study population comprised patients undergoing groin surgery for varicose veins. Recruitment was based on the following criteria:

Inclusion criteria

All patients with varicosities of the greater saphenous vein (GSV) listed for saphenofemoral ligation, stripping of the GSV and phlebectomies

All patients who agreed to participate in the study and gave written informed consent for the same

Exclusion criteria

Patients whose surgery did not include a groin incision

Patients below the age of 18 years

Pregnant or lactating women

Patients with penicillin allergy

Patients receiving antibiotics for other indications

Setting

This study was conducted at a single academic vascular surgical unit of a university hospital, the Hull Royal Infirmary, Hull, in East Riding of Yorkshire, North East England. Recruitment and randomization took place between May 2003 and December 2005. The majority of patients with varicose veins were referred to the hospital by their General Practitioners (GPs). A small proportion of patients were referred from other specialty clinics, where symptomatic varicose veins were identified, following consultation for other issues.

Patients presenting to the unit with varicose veins were given preliminary information on the trial by the consulting surgeon, during their consultation. All patients who expressed an interest in participating in the trial, or who requested further information, were provided with the study information leaflet and their details passed on to the trial team. A trial team member then contacted the potential participants with further details and where preliminary consent was obtained the participants were brought to the vascular laboratory where formal consenting and randomization was carried out. Following the consent and randomization, participants received a copy of the patient diary and full explanation on self assessment of groin wound. Opportunity was given to participants to ask questions at every stage of the process. Comprehension of both wound

assessment and diary completion was ascertained by asking participants direct closed ended questions.

At the time of recruitment and intervention, the unit had 5 consultant and 3 trainee vascular surgeons, with a case-load of approximately 600 varicose vein procedures per year. Varicose vein service at the hospital remains a predominantly consultant-led, day-case service. General anesthesia was administered by either a consultant anaesthetist, or a specialist registrar.

Sample size

The sample size calculation was based on the detection of a clinically significant reduction of wound infection rates by the administration of prophylactic antibiotics. Wound infection rates of 1.5% - 16% have been reported, following varicose vein surgery (Corder, Schache et al. 1991, Hayden and Holdsworth 2001, Hirsemann, Sohr et al. 2005). However, because varicose vein surgery is clean surgery, the expected wound infection rates should not exceed 5% (Garner, Jarvis et al. 1988). It was therefore estimated that a reduction in wound infection rate from 14% to 5% would be regarded as a clinically significant effect size.

A proposed 80% statistical power was set, with a 2-sided significance level of 5%. This provided an estimated required sample size of 190 patients in each arm (Epi Ifo version 6 statistical software; some rounding errors assumed). An estimated

15% dropout or loss to follow up was made, resulting in a target recruitment of 220 patients in each arm.

About 80% of varicose veins will affect the greater saphenous vein system (Cheatle 2005). It was thus estimated that based on the varicose vein workload of the unit, there will be about 480 referrals with varicosity of the greater saphenous vein. If 50% of referred patients consented to participation in the trial, it would take about 2 years to recruit the required sample size. It was therefore planned to complete recruitment and randomization in about 2 years.

Randomization

To ensure appropriate balance of the groups, like in all well designed and conducted RCTs, randomization was carried out. It was proposed to perform permuted block randomization to ensure a balanced allocation of number of participants to each group (Beller, Gebski et al. 2002). Blocks of 50 were derived, using computer-generated sequences and administered using sealed opaque envelopes. Patients were randomly allocated to either receiving prophylactic antibiotic (treatment group) or no antibiotic (control group). Surgeons, investigators and patients were blinded to treatment allocation.

To ensure allocation concealment, the anaesthetist, who was not part of the study team, opened randomization envelopes and administered the antibiotic (if the

patient was randomized to the treatment group), after induction of general anaesthesia. Envelopes were re-sealed using tamper-evident tape and filed in patients' medical notes.

Intervention

All suitable prospective participants were given verbal and written information on the study. Those who agreed to participate, signed an informed study consent form, and were randomized according to the earlier description.

All patients were seen preoperatively by a member of the surgical team and consented specifically for the surgical procedure. All tributary varicosities were also marked in the erect position. General anaesthesia was administered to all patients in the anaesthetic room, outside the operating room. Following induction of anaesthesia, the randomization envelope was opened, and those randomized to the treatment group were given 1.2 grams of co amoxiclav intravenously. Patients randomized to the control group received no additional medication. No member of the study team was aware of the randomization. An entry was made in the patients' drug card and anaesthetic chart to indicate that they were participating in the trial, but no mention was made as to whether or not patients received antibiotic.

The choice of co amoxiclav was according to local antibiotic prophylaxis policy for clean non-implant surgery for the hospital. Co amoxiclav is a penicillin - based

antibiotic containing a mixture of amoxicillin (as the trihydrate or as the sodium salt) and clavulanic acid (as potassium clavulanate). 1.2 grams of co amoxiclav contains 1000mg of amoxicillin and 200mg of clavulanic acid in powder form for reconstitution (BNF57 2009).

Hair removal when necessary, was done in the operating room using electric clipper, immediately before skin preparation, to reduce chances of wound infection (Tanner, Woodings et al. 2006). Skin preparation was done using neat 10% povidone-iodine solution.

All patients underwent standard sapneno-femoral junction (SFJ) ligation, stripping of the greater saphenous vein (GSV) and stab avulsion of surface tributary varicosities. The procedure has been described previously, but briefly involves dissecting the SFJ via a transverse groin crease incision, and division of all tributaries after their first division. The GSV was then flush ligated and divided at the SFJ, and the GSV was stripped to the knee using a PIN stripper. Surface varicosities were then avulsed using a Kocherised mosquito clip or vein hook via stab incisions. All groin wounds were infiltrated with bupivacaine local anaesthetic, and closed with subcuticular absorbable monofilament suture, with the application of transparent Opsite™ (Smith &Nephew, Hull, England) dressing. Stab incisions were closed with Steri-strips™ (3M, MN, USA), cotton wool, gauze and elastic compression dressings applied. This was later replaced by a thigh length TED™

anti-embolism stocking (Tyco Healthcare, Gosport, UK), which patients were advised to wear for a total of 6 weeks. All patients were discharged with Diclofenac 50mg tds to be taken regularly for 1 week and Paracetamol 1g qds for breakthrough pain. Patients were discharged with a planned follow up at 2 weeks post operatively.

Postoperative assessment and follow up

All patients were given a specifically designed diary for the recording of groin wound characteristics. Explanation and instructions on diary completion, previously given to all patients at randomisation and consent stage, were reiterated prior to discharge. Wound erythema, discharge of serous or purulent exudates and separation of wound edges were recorded on days 3, 5, 7, 9 and 10. These characteristics were based on the ASEPSIS wound scoring method, which was developed for use in trials of antibiotic prophylaxis (Wilson, Treasure et al. 1986). The ASEPSIS was developed in the mid 1980's and first used in cardiac surgery to assess infection in sternotomy and vein harvest wounds. This wound scoring system awards weighted scores for 7 components (4 wound parameters and 3 related criteria) of a wound infection. These are: the use of **A**dditional treatment (antibiotics, incision and drainage of abscess, or wound debridement); discharge of **S**erous exudates; wound **E**rythema; discharge of **P**urulent exudates; **S**eparation of tissues; **I**solation of bacteria; prolongation of **S**tay in hospital for wound problems.

Wound parameters of discharge of serous exudates, erythema, discharge of purulent exudates, and separation of tissues were assessed and scored on each day of assessment. Additional treatment, isolation of bacteria and prolongation of hospital stay were assessed and scored once during the period of the study.

It was necessary to make some adaptations to the scoring method to facilitate its use in day case setting. These included the use of patient-completed questionnaires / diaries for wound assessment, a method previously shown to be reliable and valid (Mitchell, Swift et al. 1999). Other adaptations included:

Fixed assessment time points – In the original ASEPSIS method, the 4 wound parameters were assessed and scored on 5 of the first 7 post op days (although some observations were made on day 10, when a weekend intervened, as no observations were made on weekends). In this study, patients assessed their wounds on 5 prescribed time points in the first 10 post op days (days 3, 5, 7, 9, & 10), recoding details in a wound diary which contained specific closed questions.

Scoring method – The original ASEPSIS awarded scores according to the proportion of the wound affected by each parameter, such that the presence of purulent exudates on any day for example, was awarded a score of 0, 2, 4, 6, 8, or 10, if 0%, <20%, 20% - 39%, 40% - 59%, 60% - 79%, or >80% respectively, of the wound was affected. It was decided at the design stage, not to rely on patients to

give a valid quantitative assessment of proportions of wound affected, so a fixed score was awarded for the presence of each of the wound features. Therefore, on any day of assessment, the presence of purulent exudates, the presence of serous exudates, erythema, or separation of wound edges, was awarded a score of 6, 3, 3, or 6 respectively. These are equivalent to the scores awarded by the original ASEPSIS, if 40% - 59% of the wound was affected. Although this adaptation may slightly reduce the responsiveness of the scoring system, but being a randomized trial, it was considered that there would be no bias.

For operations performed as day-cases, admission to hospital post operatively for a wound problem was regarded as prolongation of hospital stay, as was delayed discharge of in-patients due to wound problems.

For the other ASEPSIS criteria of additional treatment (antibiotics, drainage of pus, wound debridement), isolation of bacteria and prolongation of hospital stay, scores identical to the original ASEPSIS were awarded. Therefore, scores of 10, 5, and 10 were awarded for antibiotics, drainage of pus and wound debridement respectively. Isolation of bacteria scored 10, and prolongation of stay scored 5. As in the original ASEPSIS, the 4 wound parameters were scored on each day of assessment, while the other criteria were scored once during the period of observation.

The ASEPSIS generates a daily wound parameter score, which is a sum of all scores awarded for the presence of the wound features on each day of assessment. In this trial, the maximum possible daily wound parameter score was 18 and so maximum possible wound parameter score for the 5 days of assessment was 90. Where a patient had no wound problems, a score of 0 was awarded. Although the original ASEPSIS method did not utilize a daily score, it was decided that calculating a daily wound score would permit a detailed examination of the data, identifying the time points at which wound complications were most likely to occur, and the relative prevalence of each of the 4 wound parameters at each time point.

A total ASEPSIS score was calculated by summing daily wound scores for all 5 assessment days, together with any score for the other ASEPSIS criteria. In this trial, the maximum possible total score was 130. This could only have been achieved where a patient had maximum daily wound score on every day of assessment, and also received antibiotics postoperatively, underwent incision and drainage of a wound abscess, followed by wound debridement under general anaesthesia, and whose wound culture was positive for bacteria, and who was admitted to hospital with wound problems. The total score categorizes wound outcomes into satisfactory healing (score of 0-10), disturbed healing (11-20), minor

wound infection (21-30), moderate wound infection (31-40), and major wound infection (>40).

A formal postoperative wound assessment was performed on day 14 by a blinded investigator. At this assessment, diaries were collected, and information on General Practitioner (GP) attendance for wound – related problems and requirement of antibiotic for perceived wound infection, was recorded. Information on GP attendance was obtained from patients, and no independent confirmation was obtained from GPs. As the post operative assessment took place after only 2 weeks, recall was not a problem, and all patients were able to recall attendance at GP surgery, as well as which (if any) medications they received.

Microbiological swab assessment where indicated, was left to the discretion of the GP or attending physician, in patients presenting with wound problems. Unblinding of patient and investigator took place at the end of the postoperative assessment, when the re-sealed randomization envelope was re-opened.

Outcome measures

Primary:

The incidence of wound complications, determined by an adapted version of the ASEPSIS wound scoring system.

Secondary:

Visit to the GP for a wound related problem, as well as the requirement of antibiotics in the postoperative period for a perceived wound infection.

Tertiary:

The factors / variables associated with a an increased likelihood of wound complications, as determined by univariate and multivariable analyses

Statistical analysis

Data analysis was performed on an intention-to-treat basis, using SPSS for Windows version 12 (SPSS Inc., Chicago IL) and GLIM4 statistical packages. Inter-group analysis was performed using Mann Whitney test for continuous data and Chi square test for categorical data. Two-sided significance level was set at $p<0.050$. Statistical advice was provided by Dr Alan Rigby of the Academic Cardiology department, University of Hull.

The primary outcome measure was a composite assessment, measured by calculating the daily wound parameter scores, and then generating the total ASEPSIS score by summing all the daily scores as well as the scores for additional treatment, isolation of bacteria and prolongation of hospital stay. The scores for each group were compared by parametric tests. As recommended in literature

(Perneger 1998) no adjustments were made in the p-values for multiple comparisons, but unadjusted p-values are reported.

The relationship between the primary outcome measure and the explanatory variables was assessed by logistic regression from which odds ratios (ORs) and 95% confidence intervals (CIs) were estimated. The OR is an approximation to the relative risk (Morris and Gardner 1988, Rigby 1999). Model building was based on backwards elimination (p for entry=0.05; p for removal=0.1), as this is preferable to forward selection (Sauerbrei 1999). Models were validated using re-sampling based on 10-fold cross-validation (Brieman and Spector 1992). The data was divided into 10 subsets of approximately equal size while maintaining the frequency of the primary outcome measure within each of the subsets. For each subset, a statistical model was generated using backwards elimination leaving out one subset at a time. Thus, for model 1 subset 1 was left out basing the analysis on the other 9 subsets and so on (Sauerbrei 1999). The frequency of the significant variables was tabulated for each of the 10 models. A final multivariable model was generated based on variables appearing in most subsets.

Ethics

Prior to the commencement of this trial, ethical approval was sought and obtained from the Hull and East Riding Local Research Ethics Committee. Ethical approval

was granted on 23rd September 2002 (ref LREC/08/02/135). The trial registry was available at www.controlled-trials.com (ISRCTN number 12467340).

4. RESULTS

4.1. Study 1: An analysis of the suitability for endovenous ablation in patients with lower limb varicose veins

Over the 12 month study period, 482 patients were added to the day case waiting list for varicose vein surgery. 328 (68%) were women, and 154 (32%) men; median age was 44 (IQR 36 – 56) years.

339 patients (70%) were listed for primary unilateral SFJ ligation, GSV strip and stab avulsions, and so formed the cohort from which patients were selected. The remaining 30% of patients on the list (n = 143) were excluded for not meeting the primary inclusion criterion. These patients were listed as follows (figure 1.1)

Short saphenous varicose vein surgery - 6% (n = 29)

Redo surgery - 9% (n = 43)

Bilateral varicose vein surgery - 15% (n = 71)

150 of the 339 patients listed for primary unilateral SFJ ligation, GSV strip and stab avulsions, were invited for duplex scanning, and 112 (75%) attended.

According to the set suitability criteria, 63 patients (56%) were found suitable for endovenous therapy, while 49 patients (44%) were found unsuitable as follows:

19 patients had an incompetent proximal thigh branch in addition to an incompetent GSV

10 patients had a GSV diameter of <5mm at the knee

6 patients wanted general anaesthesia

1 patient preferred open surgery

1 patient had no demonstrable SFJ incompetence or GSV reflux on duplex scan

12 patients were unsuitable for a combination of reasons, mainly a small perigenicular GSV and incompetent thigh tributary (figure 1.2).

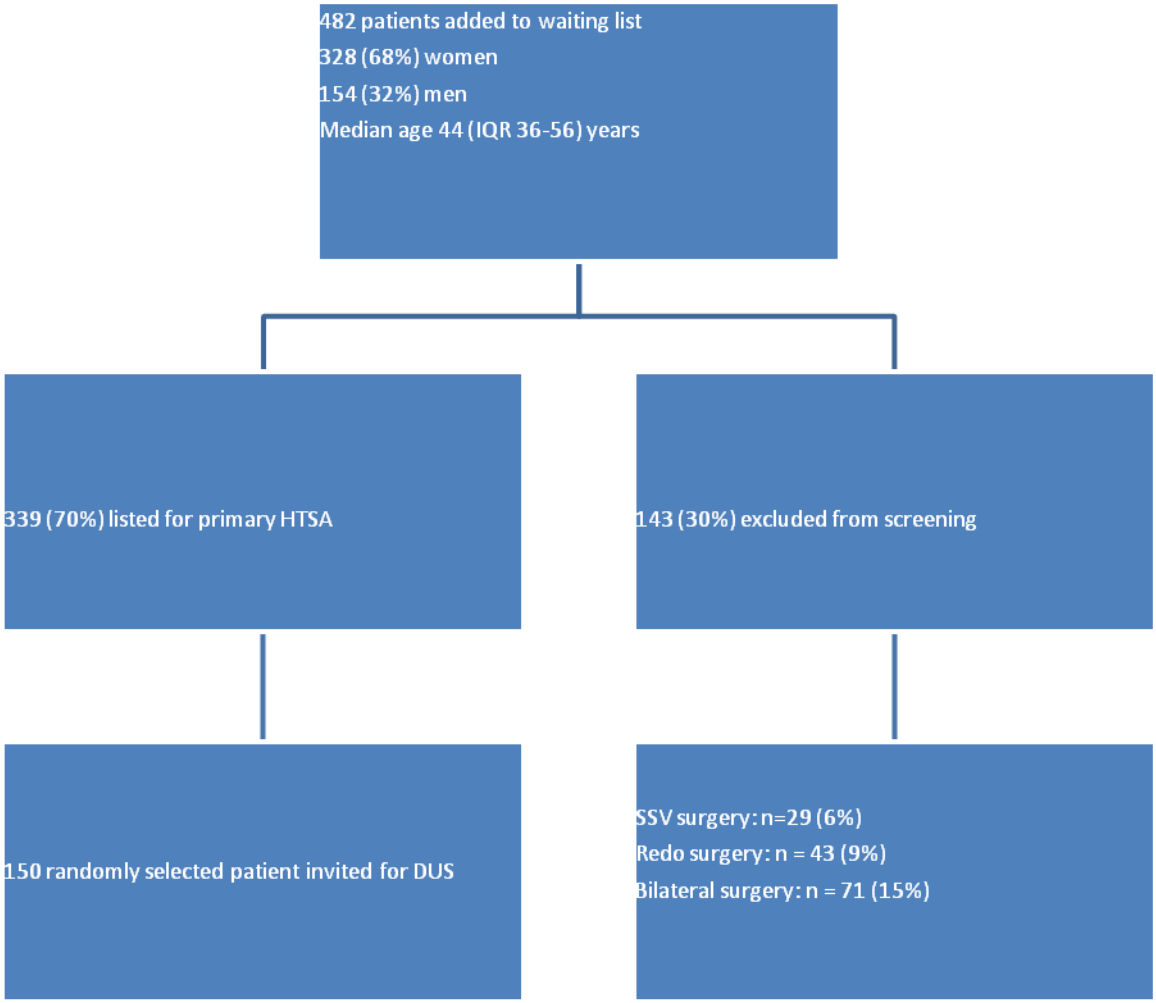

Figure 1.1 Flow chart of study 1. IQR interquartile range; HTSA high tie, strip and avulsions; SSV small saphenous vein; DUS duplex ultrasound scan. Figures are numbers of invited patients; figures in parenthesis are percentages of the group of patients in that arm.

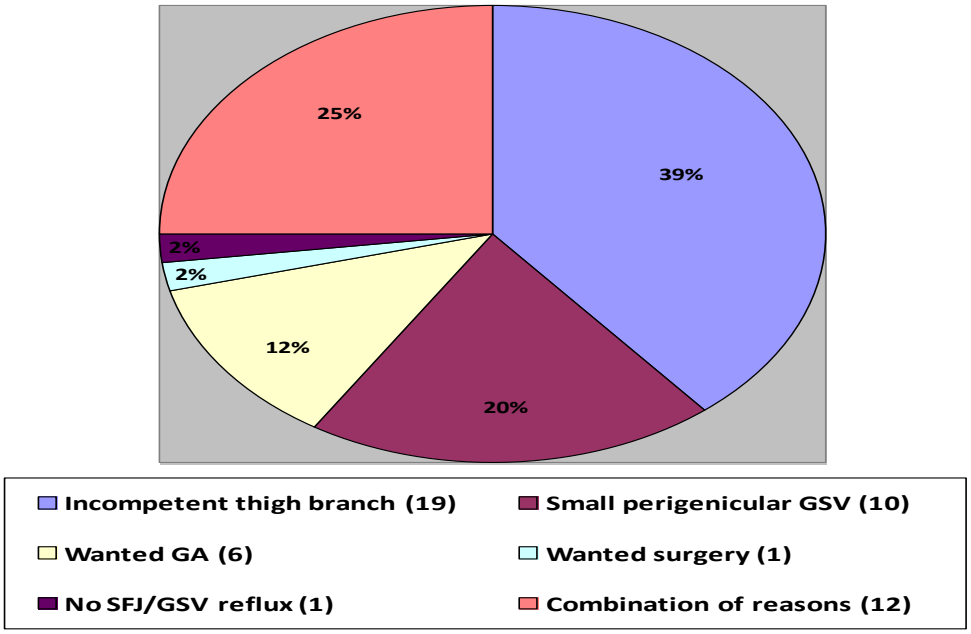

Figure 1.2 Reasons for unsuitability for EVLA. GA general anaesthetic; SFJ sapheno femoral junction; GSV great saphenous vein . Figures in legend are the actual number of patients in each category. Total number of unsuitable patients is 49

4.2 Study 2: An analysis of the feasibility and acceptability of EVLA and ambulatory phlebectomy in patients with lower limb varicose veins

The study population comprised 67 patients, 31 men and 36 women; median age 49 (IQR 35 – 58) years. CEAP class was C2 = 45, C4 = 24, C5 = 1. 70 unilateral EVLA procedures were carried out in these patients (3 patients with bilateral varicose veins underwent staged procedures).

Assessments and follow up

Patient follow up was 100% at 1 week (n = 70 limbs) and 97% at 6 weeks (n = 68 limbs); 1 patient was lost to follow up, while 1 patient missed appointment but turned up for the 12 week visit. 70% (n = 49 limbs) had been seen at 12 weeks follow up, when results were analysed.

Outcomes

Pain scores (figure 2.1)

Median pain score on day 1 was 1.6 (IQR 0.3 – 4.8); on day 4 was 0.3 (IQR 0 – 1.4) and on day 7 was 0.2 (IQR 0 – 1.1).

Occlusion rates (figure 2.2)

GSV occlusions rate was 98.6% (69 of 70 limbs) at 1 week, and 95.9% (47 of 49 limbs) at 12 weeks. SFJ occlusion was seen in 97.1% (n = 68 of 70) of limbs at 1 week and 95.9% (n = 47 of 49) of limbs.

Subsequent treatment

Three limbs (4.4%) in three patients required injection sclerotherapy after 6 weeks, for residual varicosities. All 3 patients had thread veins. 1 patient (1.4%) underwent re-do phlebectomy for residual varicosities.

Patient satisfaction (figure 2.3)

Median patient satisfaction with cosmetic appearance was 9.6 (IQR 9.2 – 10) and for overall satisfaction with treatment was 9.8 (IQR 9.5 – 10).

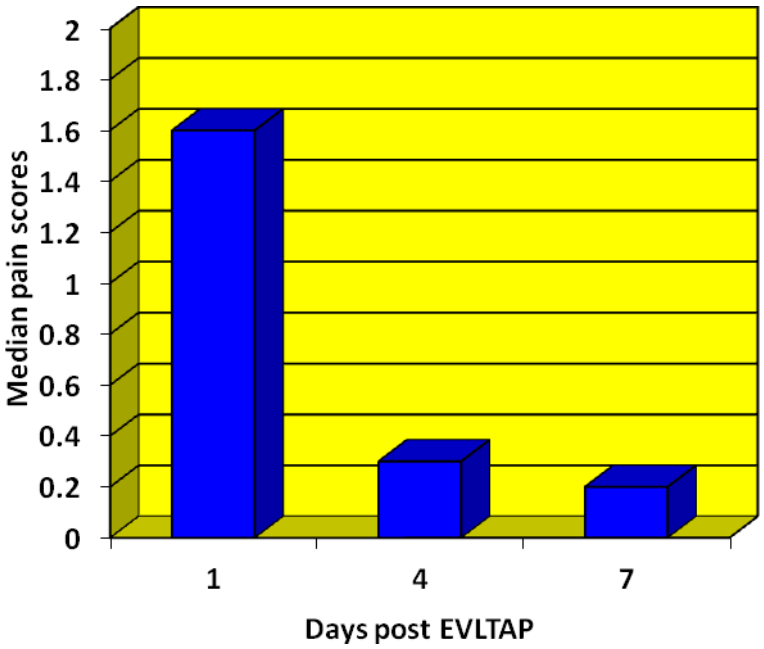

Figure 2.1 Median pain scores, post EVLTAP. Pain assessed by visual analogue scale from 0 (no pain) to 10 (maximum pain).

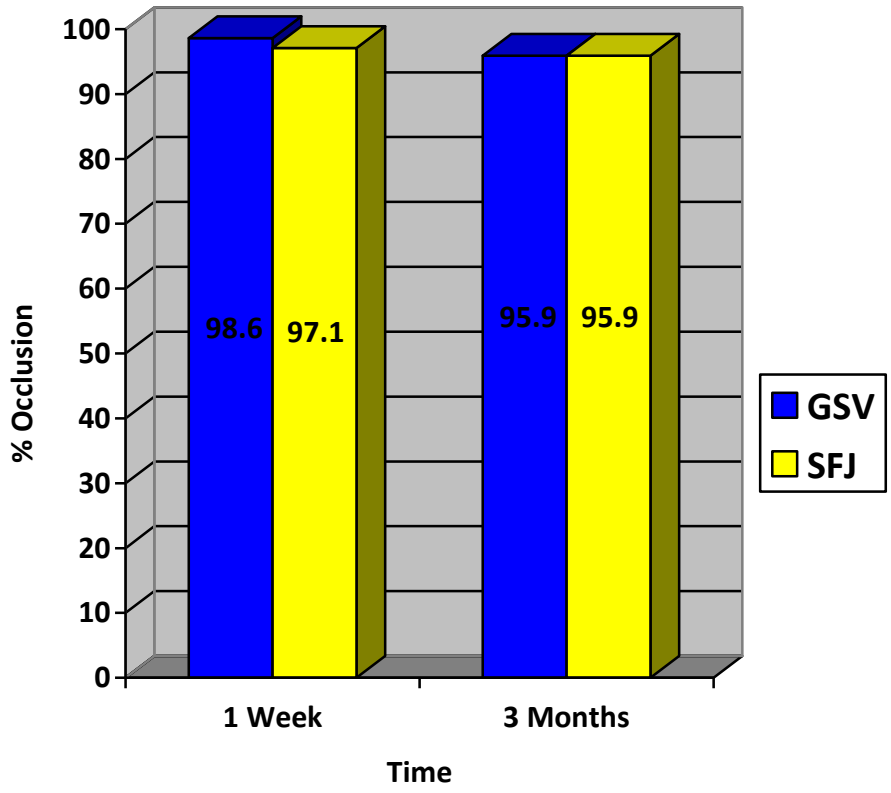

Figure 2.2 Occlusion rates post EVLTAP. GSV Great saphenous vein; SFJ sapheno femoral junction. Percentages are proportions of limbs assessed at both time points: 70 limbs at 1 week and 49 limbs at 3 months

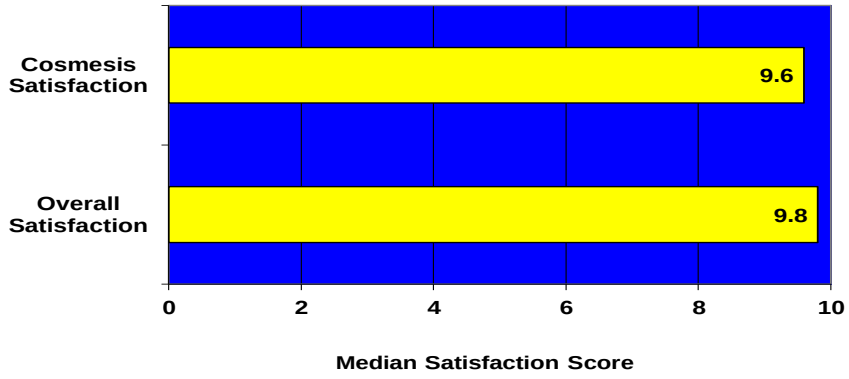

Figure 2.3 Patient satisfaction post EVLTAP. Satisfaction was assessed by a visual analogue scale from 0 (completely dissatisfied) to 10 (completely satisfied)

4.3. Study 3: A non randomised controlled trial of endovenous and surgical treatment of patients with varicose veins

Patients

Surgery Group: 62 patients were recruited; 19 men and 43 women, median age 49 years (IQR 35 – 61).

EVLA Group: 70 consenting suitable patients (33 men, 37 women), median age 49 years (IQR 35 – 58) were recruited into the EVLA arm.

Assessments and Follow up

At 1, 6 and 12 weeks was 100%, 85% and 47% following surgery, and 100%, 77% and 70%, following EVLT.

Outcomes

All procedures in the surgery group were successfully carried out as day cases, except for 5 patients who were admitted overnight (2 for social reasons and 3 for post op pain requiring parenteral analgesia).

All procedures in the EVLA group were performed successfully as day cases under local anaesthetic with no admissions.

There were no major complications such as skin burns, DVT, arteriovenous fistula, major vascular and nerve injuries, or severe wound infection in either group.

Occlusion rates

EVLA group: At 1 & 12 weeks SFJ occlusion rates on duplex ultrasound were 97 & 96 % respectively. GSV occlusion rates at the same time points were 99% & 96%.

Surgery group: All patients had successful stripping of the GSV. Duplex scans were not routinely performed following surgery.

Baseline parameters (Table 3.1)*:* The groups were well matched for age, gender and SF-36 domains except PF, BP and VT, where the surgery group had significantly lower baseline scores. The surgery group also had higher baseline AVVQ and VCSS scores.

SF-36 results

Surgery group (Table 3.2): At 1 week, there was a statistically significant deterioration in the SF-36 domains of PF, RP, BP and SF. Over the total study period, all domain scores equalled or surpassed baseline scores with statistically significant improvement in the PF, RP, BP, VT, SF and MH domains.

EVLA group (Table 3.3): There was no significant deterioration seen in any domain at 1 week. Over the total study period, all domain scores equalled or surpassed

baseline scores with statistically significant improvement in the PF, RP, BP, GH, VT and SF domains.

Intergroup comparison (Figures 3.1 – 3.4): At 1 week scores in the PF, RP, BP and SF domains were significantly worse in the surgery group. At 6 weeks scores in the PF and RP domains remained significantly worse in the surgery group, however at 12 weeks, there were no differences in any of the SF36 domains between groups.

AVVQ results

Surgery group (Table 3.2): At 1 week there was a significant deterioration in AVVQ. Over the total study period, a significant improvement in AVVQ score was observed, falling to a median value of 4.4 at 12 weeks representing a 74% improvement from baseline.

EVLA group (Table 3.3): At 1 week there was a significant deterioration in AVVQ. Over the total study period, a significant improvement in AVVQ score was observed, falling to a median value of 0.6 at 12 weeks representing a 95% improvement from baseline.

Intergroup analysis (Figure 3.5): At 1 week there was no significant difference in AVVQ scores between the two groups. At 6 and 12 weeks the EVLT group demonstrated significantly better AVVQ scores than the surgery group.

VCSS results

Scores were assessed in both groups at baseline and at 12 weeks.

Surgery group (Table 3.2): Significant improvement was observed with VCSS scores falling from 6 (4 – 8) at baseline, to 0 (0 – 1) at 12 weeks.

EVLA group (Table 3.3): Significant improvement was observed with VCSS scores falling from 4 (3 – 5) at baseline, to 0 (0 – 1) at 12 weeks.

Intergroup analysis (Figure 3.6): Demonstrated no difference in scores between groups at 12 weeks.

Parameter	Surgery	EVLA	P value
Age	49 (35,61)	49 (35,48)	.671
Sex	M = 19 F = 43	M =33 F = 37	.083
Physical Function (PF)	80 (55,91)	90 (80,100)	.003
Role Physical (RP)	75 (50,100)	100 (25,100)	.630
Bodily Pain (BP)	52 (51,74)	74 (51,84)	.009
General Health (GH)	77 (70,87)	82 (62,92)	.142
Vitality (VT)	60 (40,80)	73 (60,80)	.009
Social Function (SF)	88 (62,100)	100 (75,100)	.057
Emotional Role (RE)	100 (66,100)	100 (100,100)	.486
Mental Health (MH)	84 (67,92)	88 (76,92)	.239
AVVQ	16.6 (12.6,20.6)	11.1 (8.9,17.4)	.001
VCSS	6 (4,8)	4 (3,5)	.000

Table 3.1 Baseline Parameters. Values are Median (IQR). AVVQ-Aberdeen Varicose Vein Questionnaire; VCSS-Venous Clinical Severity Score

Measure	Pre Op	1 week	P* value (Pre op to 1 week)	6 weeks	12 weeks	P** value (Across all time points)
AVVQ	16.6 (12.6-20.6)	22 (18.1-26.7)	.001	13.2 (7.9-17.7)	4.4 (1.8-9.9)	.000
VCSS	6 (4-8)				0 (0-1)	.000
PF	80 (55-91)	40 (18-75)	.000	85 (60-95)	95 (87-100)	.000
RP	75 (50-100)	0 (0-25)	.000	100 (0-100)	100 (100-100)	.000
BP	52 (51-74)	41 (31-62)	.000	74 (62-100)	74 (52-100)	.000
GH	77 (70-87)	80 (66-87)	.483	82 (67-93)	82 (64-91)	.132
VT	60 (40-80)	55 (38-70)	.069	65 (50-80)	70 55-85)	.000
SF	88 (62-100)	63 (37-75)	.000	100 (68-100)	100 (87-100)	.000
RE	100 (66-100)	100 (66-100)	.551	100 (66-100)	100 (100-100)	.869
MH	84 (67-92)	84 (68-92)	.873	88 (72-92)	88 (80-100)	.001

Table 3.2 Quality of Life outcomes following surgery. Values are Median (IQR).

Measure	Pre Op	1 week	P* value (Pre op to 1 week)	6 weeks	12 weeks	P** value (Across all time points)
AVVQ	11.1 (8.9-17.4)	15.7 (12.6-22.3)	.000	4.7 (2.2-6.7)	0.6 (0-4.4)	.000
VCSS	4 (3-5)				0 (0-1)	.000
PF	90 (80-100)	90 (90-100)	.070	100 (90-100)	100 (86-100)	.001
RP	100 (25-100)	75 (0-100)	.037	100 (75-100)	100 (81-100)	.000
BP	74 (51-84)	72 (42-84)	.106	84 (73-100)	92 (72-100)	.000
GH	82 (62-92)	82 (72-92)	.227	86 (74-97)	82 (73-97)	.007
VT	73 (60-80)	70 (55-80)	.370	75 (60-90)	75 (60-85)	.001
SF	100 (75-100)	88 (75-100)	.033	100 (75-100)	100 (75-100)	.008
RE	100 (100-100)	100 (100-100)	.439	100 (100-100)	100 (100-100)	.039
MH	88 (76-92)	88 (76-92)	.996	88 (80-92)	90 (70-96)	.167

Table 3.3 Quality of Life outcomes following EVLA. Values are Median (IQR)

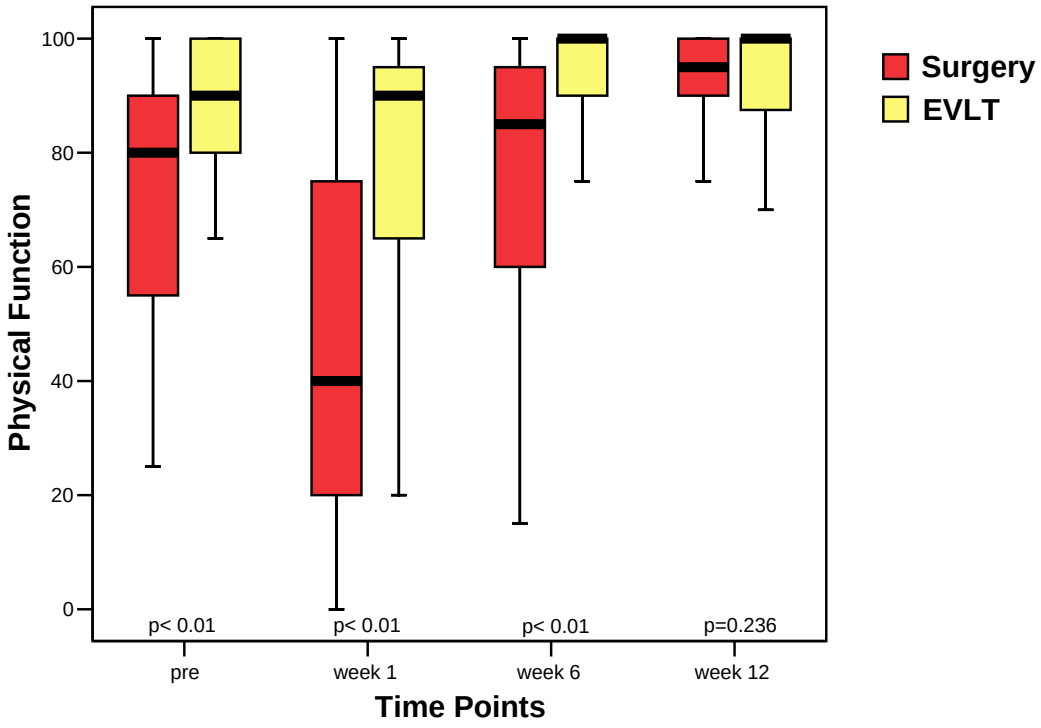

Figure 3.1 Intergroup comparison of Physical Function (PF) domain of the SF 36. Box represents IQR; line within box represents median value; whiskers represent maximum and minimum values. No outliers present within data set

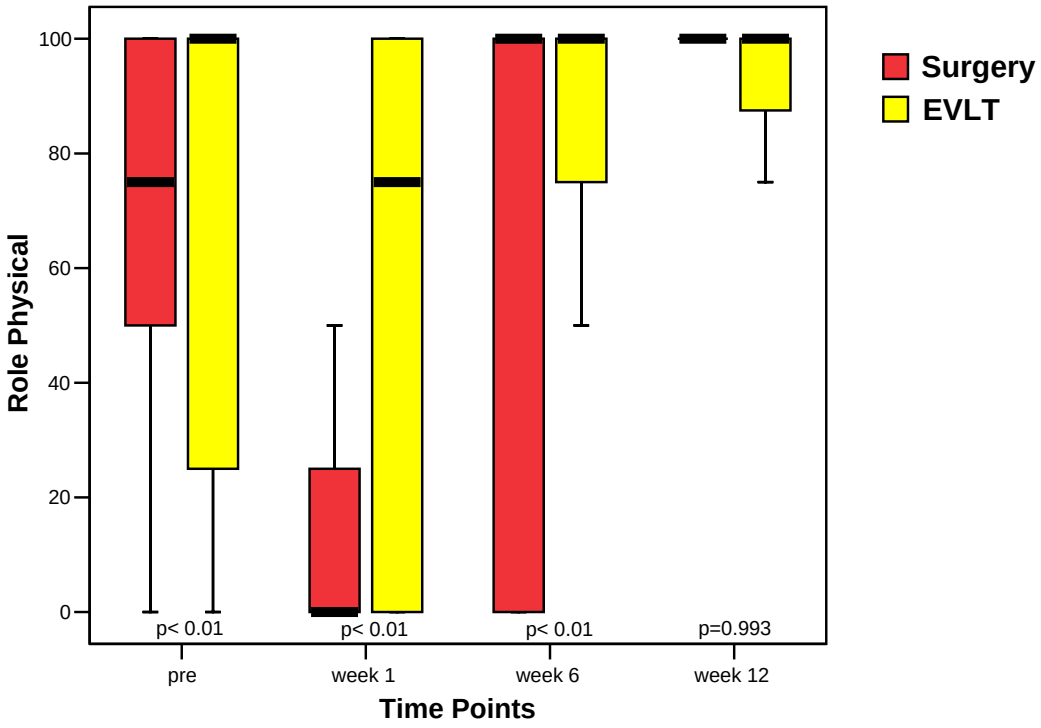

Figure 3.2 Intergroup comparison of Physical Role (RP) domain of the SF 36. Box represents IQR; line within box represents median value; whiskers represent maximum and minimum values. No outliers present within data set

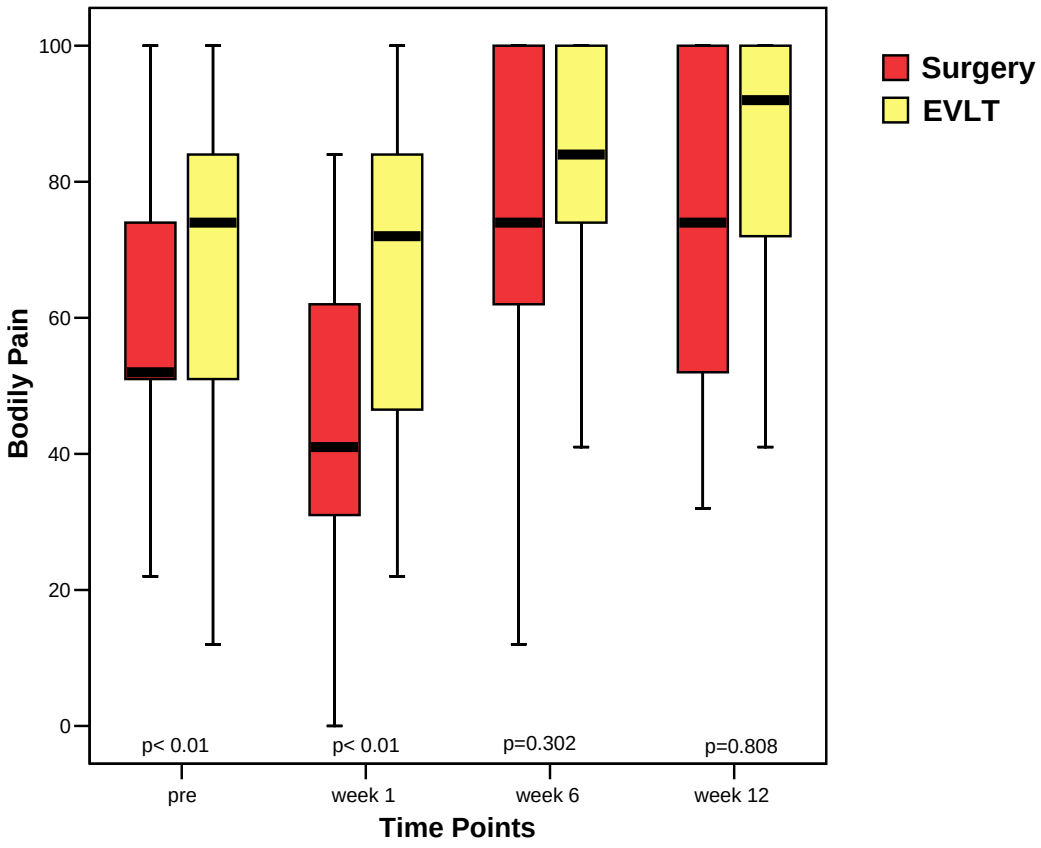

Figure 3.3 Intergroup comparison of Bodily Pain (BP) domain of the SF 36. Box represents IQR; line within box represents median value; whiskers represent maximum and minimum values. No outliers present within data set

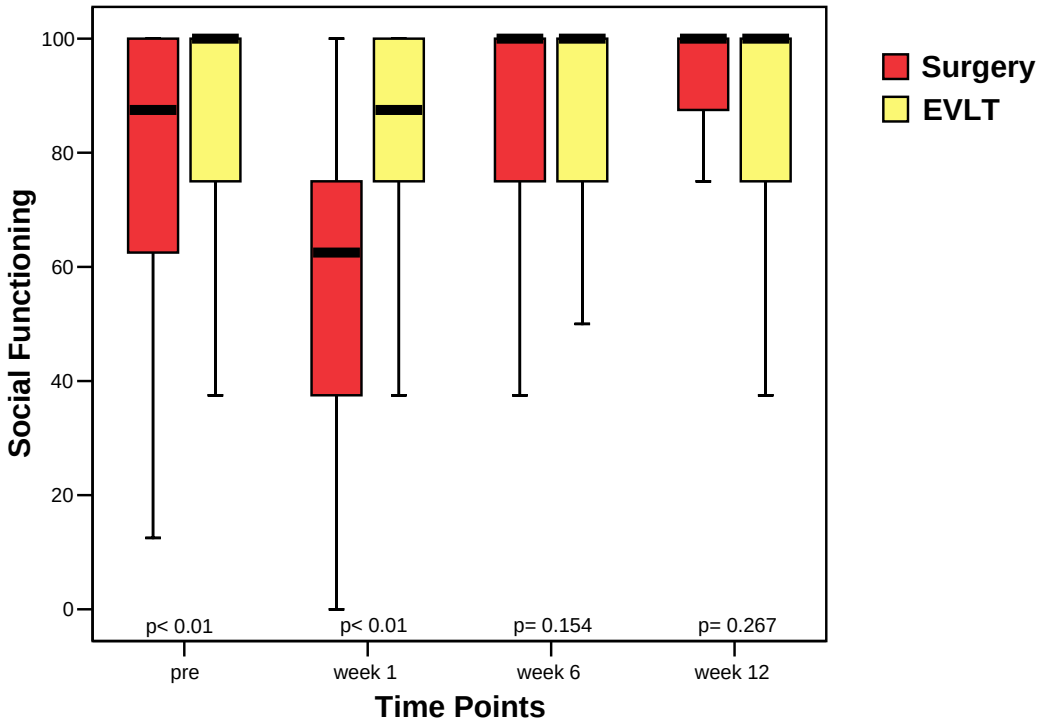

Figure 3.4 Intergroup comparison of Social Functioning (SF) domain of the SF 36. Box represents IQR; line within box represents median value; whiskers represent maximum and minimum values. No outliers present within data set

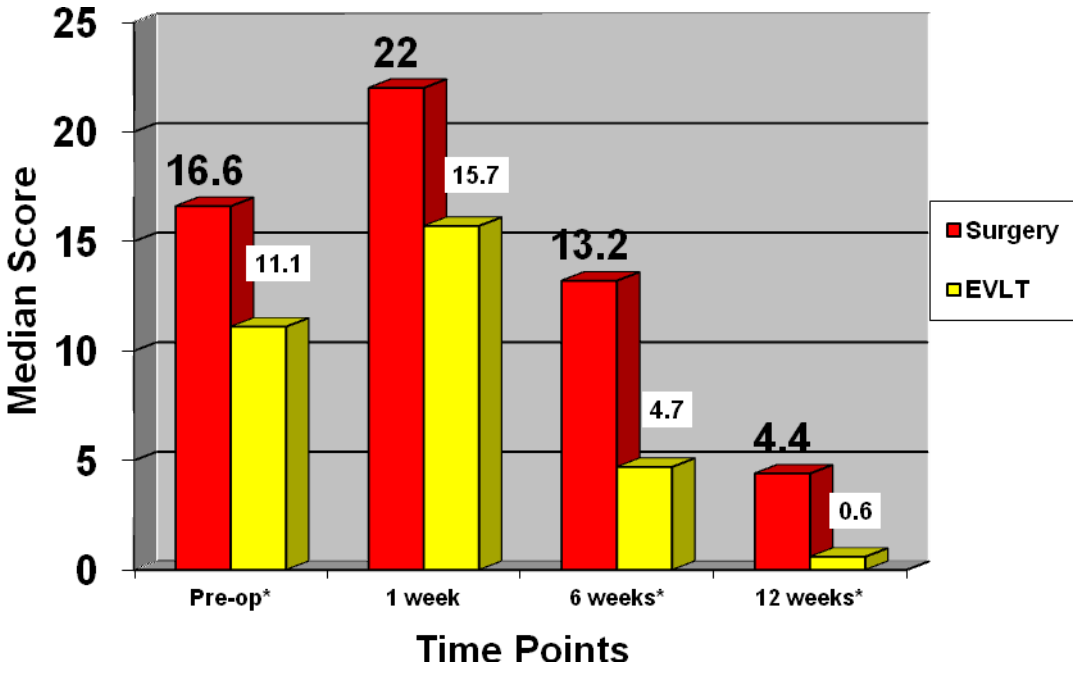

Figure 3.5 Intergroup comparisons of the Aberdeen Varicose Vein Questionnaire (AVVQ) scores. * indicates statistically significant difference

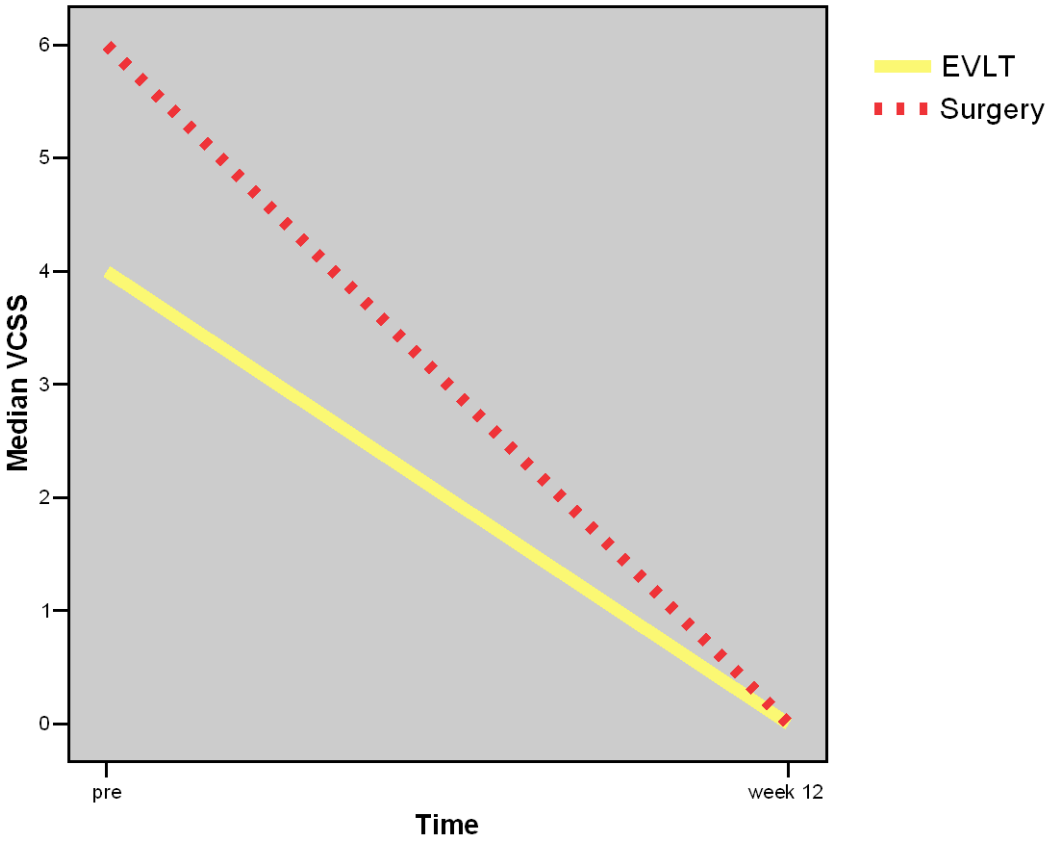

Figure 3.6 Venous Clinical Severity Scores (VCSS) in both groups at baseline, and 12 weeks post treatment. Median scores decreased to 0 in both groups, at 12 weeks post treatment.

4.4. Study 4: A randomised controlled trial of prophylactic antibiotics in patients undergoing surgical treatment of varicose veins

It was estimated that recruitment would be completed in about 24 months, but it took 31 months to complete recruitment. In this period, 456 patients were approached to enter the trial. 454 patients agreed to participate, while 2 patients declined. 11 other patients were excluded based on the preset exclusion criteria. A total of 443 patients were therefore randomized. All the randomized patients received their allocated treatment.

All treated patients whose data were incomplete (failed to attend follow up clinic and/or return wound diary, or missing diaries) were excluded from the final analysis. 212 and 214 patients were analysed in the treatment and control groups respectively. The overall attrition rate was about 4%. The consort diagram (figure 4.1), shows the flow of patients in the study. The groups were well balanced, as shown in table 4.1.

ASEPSIS Scores

Total ASEPSIS Score

Not surprisingly, varicose vein surgery being clean surgery, the majority of patients in both groups (80.6% treatment group; 67.3% control group) had total ASEPSIS score of ≤10 (indicating satisfactory healing; table 2). Overall however, significantly higher total ASEPSIS scores were recorded in the control

group, with median (inter-quartile range) score of 6 (0 – 15), versus 3 (0 – 9) in the treatment group; p = 0.013 (figure 4.2). 21 patients (9.9%) in the treatment group and 39 (18.2%) in the control group had total ASEPSIS score ≥ 21, which by ASEPSIS criteria, defines wound infection.

ASEPSIS Component Scores

The data was broken down into the various components of the ASEPSIS as described in the methods. The various component scores are as follows:

Additional Treatment

The requirement for antibiotics post operatively is reported below in section 4.3.

Two patients (0.9%) in the control group were admitted with groin wound abscess, and both underwent incision and drainage. No patient in the treatment group was admitted, and none required incision and drainage. No patient in either group required debridement of a severe wound infection.

Serous Discharge

The experience of serous discharge from the groin wounds was analysed on each day of assessment (3, 5, 7, 9 and 10). The greatest numbers of patients experiencing serous discharge occurred on day 3 in both groups (7.5% in the treatment group, and 9.3% in control group; p = 0.51). There was no difference in this outcome, between groups at anytime of observation.

Wound Erythema

This was again assessed on days 3, 5, 7, 9 and 10. The experience of wound erythema was similar in both groups, except on day 7, when significantly more patients in the control group reported wound erythema. As with serous discharge, the greatest number of patients reported erythema on day 3.

Purulent Discharge

Purulent discharge from wounds was proportionately more common in the control group at each time point, reaching statistical significance on days 3 (8.9%, vs. 3.8% p = 0.032), 5 (11.2% vs. 3.8%, p = 0.004), and 7 (12.1% vs. 2.8%, p = 0.001) in the control and treatment groups respectively. In all, 43 (20.1%) in the control group and 22 (10.4%) patients in the treatment group discharged purulent exudates on at least one day during the period of observation. This difference was significant (p = 0.005).

Separation of Wound Edges

There were proportionately more patients in the control group reporting separation of wound edges in the control group, on each day of assessment. The difference however, did not reach statistical significance at any time point.

Isolation of Bacteria

As stated in the methods section, the decision to swab wounds was left to the discretion of the GPs or attending practitioner in patients presenting with wound

problems in the post operative period. Overall, four wounds were swabbed for microbiological cultures in the treatment group, of which 1 (25%) was positive (*Staphylococcus epidermidis*). In the control group, 5 of 10 cultures (50%) grew *Staphylococcus aureus.*

Prolongation of Stay

There was no delayed discharge from hospital as a result of wound issues in either group. As stated earlier, 2 patients (0.9%) were admitted post operatively for incision and drainage of groin wound abscess.

The results of the daily ASEPSIS wound component assessment are summarised in table 4.3, while the proportion of patients with daily total wound scores >10 is summarised in table 4.4; these show that daily scores were significantly higher (indicating worse wound outcome) in the control group, as compared with the treatment group.

Day 14 Assessment

There were no significant wound differences between the groups as assessed by a blinded observer using ASEPSIS criteria on day 14 (table 4.5).

General Practitioner (GP) Attendance

Thirty-four patients (16%) in the treatment group reported visiting their GP post operatively for problems in their groin wounds, compared with 52 patients (24.3%) in the control group. Thus patients receiving prophylactic antibiotic,

were significantly less likely to visit their GP (OR 0.595; 95% CI 0.369 – 0.961; p = 0.034).

GP Prescription of Antibiotics

Treatment group patients were less likely to receive antibiotics in the postoperative period for a perceived wound infection: 10 patients (4.7%) versus 29 patients (13.5%) (OR 0.316; 95% CI 0.152 – 0.657; p = 0.002).

Logistic Regression Analyses

Univariate Analysis

The results of the univariate analysis are shown in table 4.6. Univariate analysis showed that receiving antibiotics was associated with the odds of a good outcome, defined as satisfactory healing (a total ASEPSIS score of ≤ 10). Increasing BMI was associated with a poorer outcome as was redo surgery. A CEAP score ≥ 4 was not significantly associated with the odds of having a poor outcome, though these patients in general had higher ASEPSIS score. There was no significant relationship between wound outcome and age. In combination, five variables (receiving antibiotics, BMI, smoking, redo surgery and gender) appeared in 10 models. Receiving antibiotics and BMI appeared in all 10, current smoking (indicative of a poor outcome) appeared in 7; redo surgery in 3, while gender appeared in 1. Several models appeared more than once.

Multivariable Analysis

The multivariable model consisted of three variables only: randomization to antibiotics (OR=2.2, 95% CI=1.3-3.6, p=0.003), BMI (OR=0.92, 95% CI=0.87-0.97, p=0.005) and current smoking (OR=0.5, 95% CI=0.3-0.9, p=0.03) which were adjusted for each other. These variables were selected as the most frequently occurring from the 10-fold cross-validation exercise.

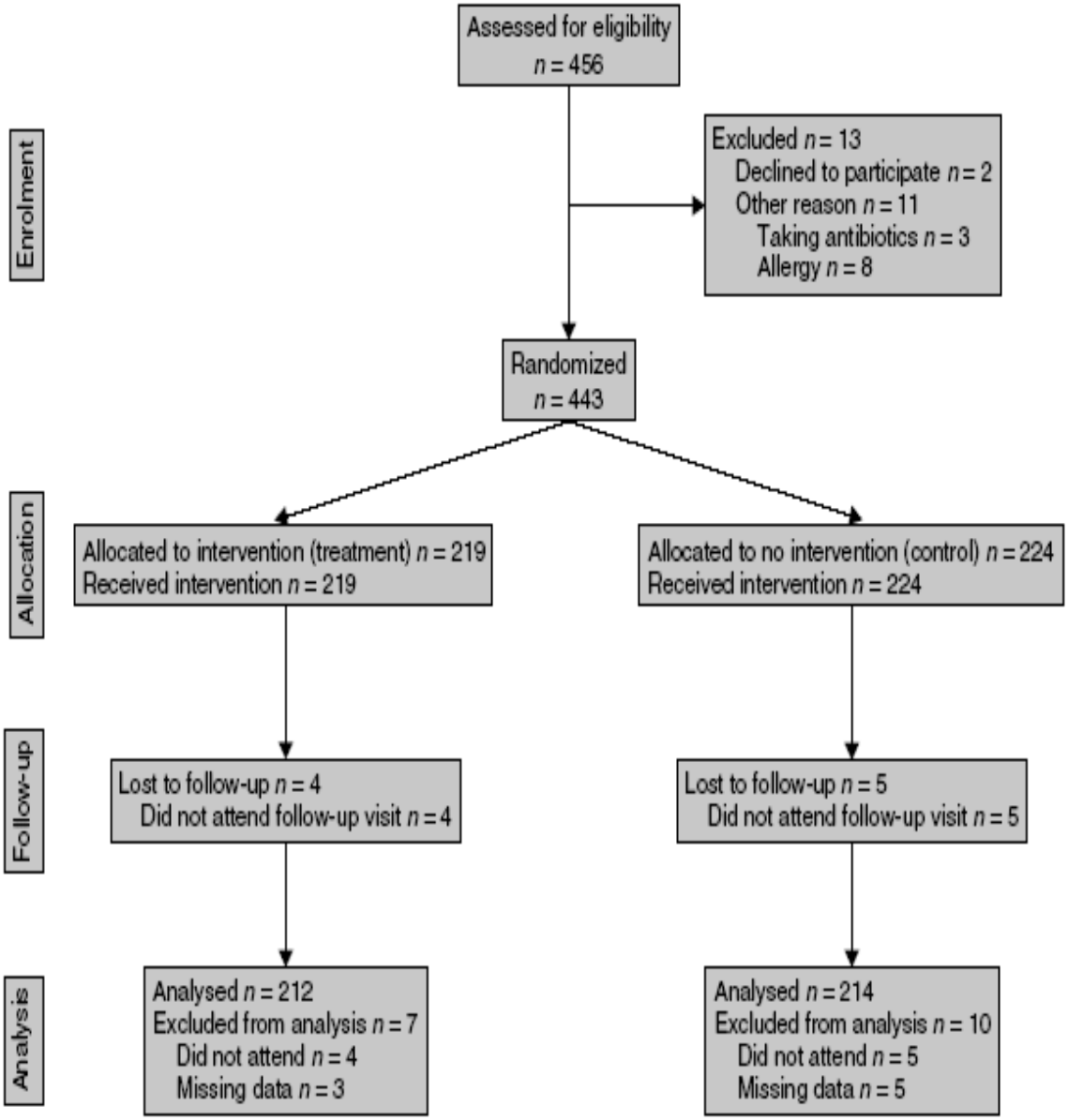

Figure 4.1 CONSORT diagram. Flow chart of participants through trial

	Treatment Group	Control Group
Number of patients	212	214
Female	143	128
Median Age (IQR)	46 (37 – 54)	49 (37 – 59)
Bilateral Surgery	65 (130 limbs)	60 (120 limbs)
Redo Surgery	28	27
Median BMI (IQR)	27 (24 – 30)	27 (24 – 29)
Current Smoking	60	41
CEAP C1	-	-
C2	150	162
C3	2	1
C4	57	47
C5	3	1
C6	-	1
Unclassified	-	2

Table 4.1 Baseline demographic data; IQR: interquartile range; BMI: body mass index; CEAP: clinical-aetiologic-anatomic-pathophysiologic (C1-telangiectasia, C2-varicose veins, C3-oedema, C4-skin changes, C5-healed ulcers, C6-active ulcers); current smoking was arbitrarily defined as smoking of at least 5 cigarettes daily for a minimum of 3 months, at the time of treatment.

ASEPSIS Score	Treatment group n (%)	Control group n (%)
0 – 10	171 (80.7)	144 (67.3)
11 – 20	20 (9.4)	31 (14.5)
21 – 30	10 (4.7)	17 (7.9)
31 – 40	5 (2.4)	6 (2.8)
> 41	6 (2.8)	16 (7.5)

Table 4.2: Stratified total ASEPSIS score; Chi-square for trend (1 df = 4.35), p=0.037

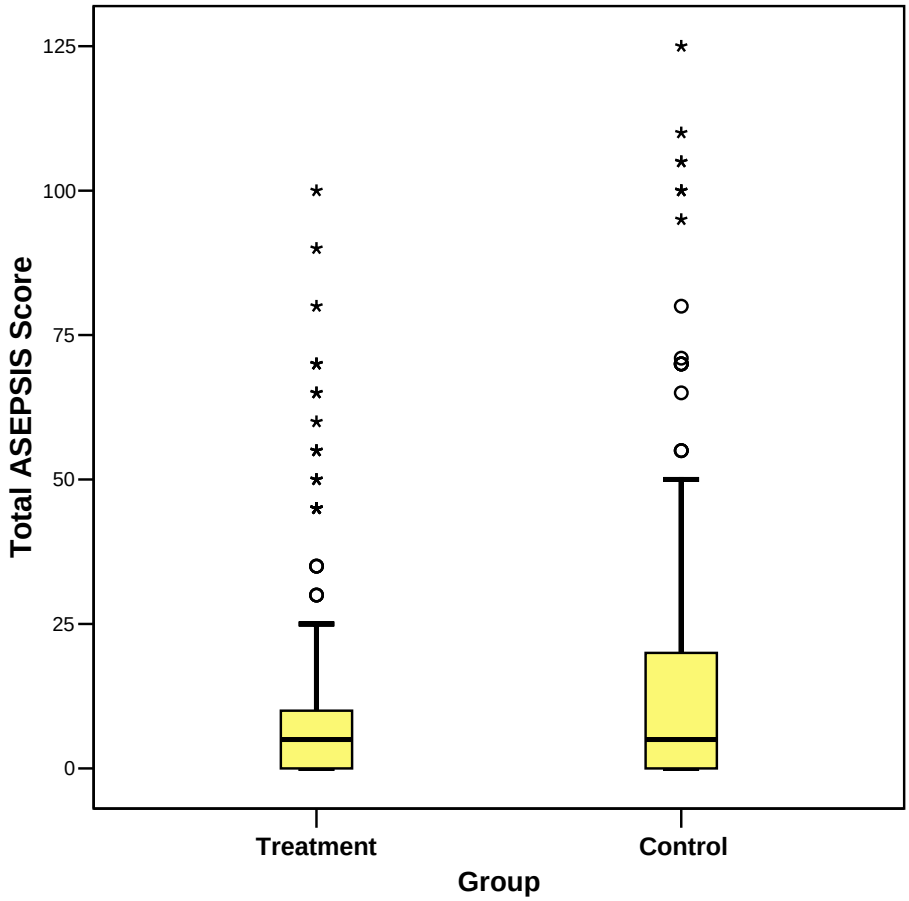

Figure 4.2: Total ASEPSIS score; bar within box represents median score; box represents interquartile range (IQR); whiskers represent 1.5 x IQR; circles represent outliers <3 x IQR, and stars represent extreme outliers >3 x IQR. The median (IQR) was 3 (0-9) and 6 (0-15) in the treatment and control groups respectively; p=0.013. Analysis done using Mann Whitney test.

Feature and Day of assessment	Groin wounds affected n (%)		P value
	Treatment group	Control group	
Erythema			
3	73 (34.4)	85 (39.7)	0.27
5	55 (25.9)	70 (32.7)	0.13
7	34 (16.0)	50 (23.4)	0.045
9	29 (13.7)	39 (18.2)	0.28
10	22 (10.4)	34 (15.9)	0.09
Serous discharge			
3	16 (7.5)	20 (9.3)	0.51
5	9 (4.2)	12 (5.6)	0.52
7	8 (3.8)	4 (1.9)	0.23
9	6 (2.8)	5 (1.9)	0.74
10	4 (1.9)	3 (1.4)	0.68
Wound separation			
3	9 (4.2)	12 (5.6)	0.52
5	12 (5.7)	17 (7.9)	0.35
7	11 (5.2)	21 (9.8)	0.07
9	14 (6.6)	18 (8.4)	0.48
10	11 (5.2)	18 (8.4)	0.19
Purulent discharge			
3	8 (3.8)	19 (8.9)	0.032
5	8 (3.8)	24 (11.2)	0.004
7	6 (2.8)	26 (12.1)	0.001
9	8 (3.8)	15 (7.0)	0.14
10	5 (2.4)	9 (4.2)	0.29

Table 4.3 Wound characteristics: Erythema, serous discharge, purulent discharge and wound separation

Day of assessment	ASEPSIS Wound Score > 10 % of patients (range of all observed scores)		P value*
	Treatment group	Control group	
Day 3	2.4 (0 – 15)	2.3 (0 – 18)	0.043
Day 5	2.4 (0 – 15)	5.6 (0 – 18)	0.032
Day 7	2.8 (0 – 18)	5.6 (0 – 15)	0.003
Day 9	2.8 (0 – 15)	5.1 (0 – 15)	0.33
Day 10	1.4 (0 – 15)	3.3 (0 – 15)	0.10

Table 4.4 Proportion of patients with daily total wound scores >10. Range of all observed scores in each group on the day, shown in parenthesis; *p value based on all daily scores; Mann Whitney test

	Treatment group n (%)	Control group n (%)	*p value
Erythema	4 (1.9)	10 (4.6)	0.107
Serous exudates	3 (1.4)	4 (1.9)	0.713
Purulent exudates	1 (0.5)	1 (0.5)	0.997
Separation	5 (2.4)	13 (6.1)	0.057

Table 4.5 Day 14 wound assessment. *Mann Whitney test

Variable	Outcome (n)		Odds ratio (95% CI)	P value
	poor	good		
Age*			0.99 (0.98-1.01)	0.55
BMI*			0.94 (0.89-0.99)	0.009
Gender				
Female	63	208	1.0	0.08
Male	48	107	0.7 (0.4-1.1)	
Redo Surgery				
No	86	261	1.0	0.16
Yes	20	35	0.6 (0.3-1.1)	
Unknown	5	19	1.3 (0.5-3.6)	
Smoking				
Never	41	139	1.0	0.08
Current	65	36	0.5 (0.6-0.9)	
Ex	20	72	1.1 (0.6-2.0)	
Unknown	14	39	0.8 (0.4-1.6)	
CEAP class				
C2-3	76	239	1.0	0.16
C4-6	35	74	0.7 (0.1-1.1)	
Unknown	0	2	X	
Randomisation to antibiotics				
No	70	144	1.0	0.002
Yes	41	171	2.0 (1.3-3.1)	

Table 4.6 Univariate analyses. * analysed as continuous variables; X not possible to estimate odds ratio due to cell zero

DISCUSSION

Varicose veins are common, and in the United Kingdom, they constitute a huge burden to the National Health Service, in terms of the surgical workload, outpatient attendances at primary and secondary health, as well as cost of management of complications (Michaels, Campbell et al. 2006). Besides the burden on healthcare resources, varicose veins also cause problems including Quality of Life limitations for sufferers, with implications for their physical, mental and economic health. The appropriate and optimal management of varicose veins is therefore both desirable and necessary, especially in the current economic climate.

This current work focused on optimizing varicose vein management. The treatment of varicose veins is evolving, with minimally invasive techniques emerging in the last few years as alternatives to conventional surgery. These are aimed at reducing surgical morbidity, shortening recovery period and providing comparable results (Beale, Mavor et al. 2004). In addition, minimally invasive techniques may offer acceptable options to the millions who have varicose veins but are unwilling or unable to undergo surgery (Min, Khilnani et al. 2003). When endovenous laser therapy (EVLT) was first introduced, it was principally a technique for treating GSV truncal varicosity. The case reports and series at that time indicated (quite correctly), that the new minimally invasive technique was likely to be safe and effective. It was therefore a technique we were quite eager to introduce in the management of our patients.

In designing our initial study, we aimed to limit technical failures during the early stages of rendering an EVLA service for varicose veins. The eligibility criteria were deliberately kept rigid and narrow. There were 339 patients listed for primary GSV surgery, making up 70% of the varicose vein surgery waiting list. This proportion, as well as the distribution of primary and secondary procedures, and the different rates of junctional incompetence, is in keeping with the general findings of patterns of lower limb varicosities in other studies (Goren and Yellin 1990, Beale and Gough 2005, Cheatle 2005).

Patients listed for re-do surgery were excluded. This group accounted for 9% of patients on the list. Although the rates of recurrent varicose veins vary widely, at least 20% of varicose vein operations are performed for recurrent disease (van Rij, Jones et al. 2004). The exact reason for a low re-do surgery list among our cohorts is unknown. Possible explanations would include: the fact that only the day-case list was screened, leaving out those listed for in-patient treatment; it may also be an indication of low prevalence of recurrent disease in our catchments area; or that our patients were not particularly bothered by recurrent varices, if they were not causing significant health – related problems. Because stripping of the GSV has been performed fairly routinely as a primary procedure, it was our view that there will be a relatively low number of patients with recurrent varicose veins who had an anatomically intact, albeit incompetent GSV; therefore, we excluded these patients, because the majority of them were thought unlikely to be suitable for EVLA. In retrospect, judging from today's practice, several of these patients with recurrent disease would have been

suitable for EVLA. Laser ablation is now routinely performed for recurrent varicose veins. There are however necessary criteria for suitability. Theivacumar and Gough recently published on EVLA for recurrent varicose veins (Theivacumar and Gough 2011). They only included patients who had at least 10cm of truncal refluxing vein, with a diameter of >3mm proximal to the varicosities. Although this was a local guideline, it was necessary to have a sufficient length of vein that could be ablated in order to abolish reflux. The presence of neovascularisation was not an exclusion criterion, but such patients did not have ablation up to the major junction (SFJ or SPJ), but about half of this cohort of patients had foam injection via the laser catheter beyond the point of EVLA. By their selection criteria, 95 of 127 (75%) patients with recurrent varicose veins were suitable for EVLA. van Groenendael and colleagues performed a retrospective analysis of patients with recurrent varicose veins of the GSV system, treated by surgery or EVLA (van Groenendael, van der Vliet et al. 2009). They excluded patients who had no identifiable connection between the superficial varicosities and the SFJ, as well as patients with a GSV <4mm. By their criteria, suitability for EVLA was only 31% of patients. Most of their anatomical unsuitability was as a result of excessive tortuosity.

In our suitability study, we also excluded 71 patients (15%) listed for bilateral surgery. Campbell and colleagues, in investigating patient preference for treatment of their varicose veins, showed that patients preferred having a single bilateral operation even if it involved in – patient treatment, to having two unilateral day case procedures (Campbell, Dimson et al. 1998). The concern at

the time, of exceeding a safe dose of local anaesthetic medication if bilateral procedures were performed at a single sitting meant exclusion of these patients. It was felt likely however, that a similar percentage of these patients will be suitable for EVLT. As technical skills have improved, the total dose of local anaesthetic use has also decreased. It is now fairly routine to perform bilateral EVLA or EVLA of the SSV and GSV at a single sitting.

29 (6%) patients with SPJ incompetence / SSV reflux were also excluded. EVLA for SSV varicosities was considered technically more difficult, with greater potential for causing harm, and its efficacy and safety had not yet been clearly demonstrated when this study was commenced. The initial reluctance by various EVLA practitioners to perform ablations of the short saphenous vein may have been related to the concerns about proximity of the sural nerve to the small saphenous vein, as well as thrombus extension into the popliteal vein (Gibson, Ferris et al. 2007). At this present time, laser ablation for small saphenous varicosity has become common place, and is in fact the preferred treatment over standard surgery, with reported better efficacy and less complications (Tellings, Ceulen et al. 2011). In comparison to laser ablation of the great saphenous vein however, treatment of the SSV is associated with more morbidity. This was recently demonstrated in our unit, in a study carried out by Carradice and colleagues, who performed a retrospective cohort analysis comparing response following treatment (both standard surgery and endovenous laser ablation) of great and small saphenous vein incompetence. They found a significantly worse deterioration in Aberdeen Varicose Vein

Questionnaire (AVVQ) Scores in the early post intervention period, with treatment of small saphenous than was observed after similar treatment of the great saphenous vein (Carradice, Samuel et al. 2011).

Theivacumar and colleagues reported in 2007, their initial experiences with EVLA of short saphenous vein varicosities (Theivacumar, Beale et al. 2007). They had good initial and 3 months technical success rates, with improved AVVQ scores at 3 months and, and minimal complication rates. They did not specify their suitability criteria, but they found 72% of patients with primary SSV varicosity, and 69% of patients with recurrent disease, suitable for EVLA. The high rate of EVLA suitability in recurrent SSV varicose veins as compared with recurrent GSV varices is presumably due to the fact that the short saphenous vein is not routinely stripped at open surgery, and therefore there is often an intact SSV which is amenable to laser ablation. Towards the end of our study, we began performing a randomised controlled trial of surgery versus EVLA for SSV incompetence, and the majority of patients were suitable for laser ablation and therefore eligible for the trial. However, at the time of initiation of the laser suitability study, it was decided to exclude patients with SSV varicosities, as EVLT at that time, was largely a procedure for the treatment of primary GSV incompetence.

While it would have been desirable to scan all eligible patients on the list, invited patients were limited to 150 as a consequence of costs. This sample size of randomly selected patients would have been a fair representation of the 339 patients on the waiting list for GSV surgery. The response rate (of invited

patients who attended for scanning) was 75%, which was an acceptable response rate. Based on our starting suitability criteria, 56% of patients (n = 63 of 112) were found suitable for EVLT. This is a little less than we expected, and the 62% eligibility which was reported by Beale et al (Beale, Mavor et al. 2004), but this was no doubt due to the strict suitability criteria used.

In exploring the causes of unsuitability, the major proportion of our patients (39%; n = 19/49) was unsuitable as a result of an incompetent major thigh tributary of the GSV. Almost all of these patients also had an associated incompetent GSV. These tributaries are often very tortuous and therefore difficult to canulate and pass a laser fibre through. In addition, with tributaries that drain into the GSV close to the SFJ, the risks of residual reflux are high, except they are also laser ablated.

10 patients (20%) had a GSV with a diameter of less than 5 mm around the knee. Such small veins were associated with a high “failure to canulate” rate. As we aimed to keep this to a minimum and avoid stab – wound / cut – down vein canulation, we were of the opinion that this exclusion criterion was essential. There is a minimum vein size to allow for cannulation and catheter insertion for laser ablation. With better skills, as well as the development of micro puncture sets, it is now possible to cannulate even small diameter veins that were excluded in the early days of laser ablation. van Groenendael et al excluded patients whose GSV was less than 4mm (van Groenendael, van der Vliet et al. 2009), while Theivacumar and Gough used a 3mm cut off (Theivacumar and

Gough 2011). In the on-going Comparison of Laser Ablation Sclerotherapy and Surgery (CLASS) multicentre trial, a minimum size of 3mm is set.

A small number of patients will always prefer a general anaesthetic (Proebstle, Lehr et al. 2002), or not want to undergo a new procedure, preferring the “gold standard” or “old and trusted”. Whilst EVLA can be performed under general anaesthesia, this would seem to negate many of its benefits such as patient feed back during the procedure, short recovery time, and immediate patient ambulation (Min and Khilnani 2005).

There are patients who may be unsuitable for more than one reason. In our cohort, 25% (n = 12) of patients were unsuitable for multiple reasons. Most common combination of reasons was a small perigenicular GSV and a refluxing antero-lateral thigh (anterior accessory GSV) branch. These patients were offered open surgery. In the present day practice of EVLA, these do not constitute non suitability for laser ablation. If an accessory anterior GSV is incompetent, it can be laser ablated so long as it is not too tortuous, and it is of adequate calibre (Theivacumar, Darwood et al. 2009, Chaar, Hirsch et al. 2011). A more proximal point of cannulation can and has been used to overcome small peri-genicular GSV.

The techniques, indications, and evidence for EVLA have evolved and advanced in the years since this study was performed. As has already been alluded to, many of the exclusion criteria set in this study are no longer considered as contraindications for EVLA. It is now routine for large thigh

tributaries / accessory saphenous veins (if not too tortuous), SSV, recurrent, and bilateral varicose veins to be treated by laser ablation (Gloviczki, Comerota et al. 2011). Several authors have reported successful ablation of the SSV, with excellent clinical outcomes and good safety profiles (Knipp, Blackburn et al. 2008, Huisman, Bruins et al. 2009). Theivacumar and Gough reported their experience with laser ablation of recurrent varicose veins of both the GSV and SSV, with similar technical and clinical success, as well as procedural complication rates as primary vein ablation (Theivacumar and Gough 2011).

As already alluded to, there have been advances in the management of varicose veins, and the recent and on-going endovascular revolution has seen 'recent technologies' quickly become 'yesterday's toy'. The main critique of the EVLA suitability study really lies with this issue of timeliness. The findings from the study have now become dated, and as already been alluded to, it would be erroneous to maintain that only about half of all varicose veins are suitable for EVLA. At the time of designing the study, endovenous laser ablation was in its infancy, and there were many who were sceptical as to the true value of this new technique. It was also, largely a procedure performed on GSV varicosities. It was therefore necessary to be perhaps over selective in the suitability criteria designed for the study. Also, because skills were only just being developed, technically "challenging" cases were deemed unsuitable. As skills have developed, these cases are now known to be suitable for EVLA.

In the present day practice of endovenous laser ablation, the combination of increased experience and technical ability, the development of improved and

more user friendly ultrasound scanners and sonographic technology, as well as newer accessories and kits such as the micro puncture kits and hydrophilic wires and catheters, it is conceivable that a significant proportion of varicose veins can be treated either in whole, or at least partly by endovenous laser ablation. While no recent study has looked at proportion of varicose veins suitable for EVLA, anecdotal evidence from daily EVLA practice would suggest that the majority of varicose veins (certainly well above the 56% in our trial) would be suitable for laser ablation.

When EVLT was introduced, the standard was to perform laser ablation of the truncal vein and leave treatment of branch / tributary varicosities for about 4 to 6 weeks (Min, Zimmet et al. 2001, Navarro, Min et al. 2001). In many cases, this remains the standard practice for laser ablation (Khilnani, Grassi et al. 2010). While this makes the procedure shorter, there is the disadvantage of repeated visits for further treatment, which is estimated to be necessary in 30% – 99% of cases (Beale, Mavor et al. 2004). This may be unappealing to patients and may reduce cost effectiveness (Campbell, Dimson et al. 1998, Kluner, Fischer et al. 2005). It was therefore appealing to explore the possibility of performing truncal vein ablation, along with phlebectomies of tributary varicosities as a combined procedure. Should this procedure be feasible, then it should not detract from the ‘minimally invasive’ nature of EVLA, and be acceptable to patients, with good efficacy and safety profile. The EVLTAP procedure was developed to address these issues.

This study demonstrated that EVLTAP did not significantly increase patient discomfort or pain. Patients in this study reported minimal pain, comparable to that reported by practitioners of staged treatments. Unlike the experience of Min and Khilnani (Min and Khilnani 2005), our patients who underwent EVLTAP did not complain of delayed tightness post procedure. This may be because non steroidal anti inflammatory medications were routinely prescribed post procedure. The absence of this delayed tightness did not translate to treatment failure.

In our experience, EVLTAP took a median time of 69 (IQR 60 – 80) minutes to perform, from vein cannulation to application of compression bandaging. This is not unduly prolonged when compared with several EVLT only series. Gerard and colleagues reported an average duration of 60 minutes to perform EVLT alone (Gerard, Desgranges et al. 2002). It is realised that length of procedure is dependent on length of treated vein and operator experience, and some authors have reported much shorter average procedure times of about 30 minutes (Christenson, Gueddi et al. 2010) . It is however, an important point to note that combining phlebectomy with laser ablation does not significantly prolong the procedure.

At 3 months scan, 2 limbs (4%) demonstrated reflux in the proximal segment of the GSV. Reflux was defined as a retrograde flow of >0.5 seconds, as recommended for superficial veins. These 2 cases were performed early in the series, and were associated with total laser energy delivery below the recommended 70 J/cm for technical and clinical success (Proebstle, Gul et al.

2003). These 2 patients went on to have repeat laser ablation. It must however be said, that a few other veins treated with less than 70 J/cm remained occluded at 3 months, thus suggesting that other factors may have contributed to the early failure. Besides the energy delivery, other factors have been suggested to lead to failure of occlusion, or early recanalisation. Prince and Colleagues studied the impact of laser fibre design on the outcome of EVLA, and found that the use of the standard bare-tip fibre was associated with a treatment failure rate of 2.3%, compared with 11.1% using the newer gold-tip NeverTouch VenaCure laser fiber (AngioDynamics, Queensbury, NY) (Prince, Soares et al. 2011). Other investigators have that a large vein size, which may be difficult to compress fully against the laser fibre with tumescent fluid, leads to treatment failure (Kontothanassis, Di Mitri et al. 2009, Myers and Jolley 2009). The use of a continuous laser mode has also been suggested to be more effective that the pulsed mode (Rasmussen, Bjoern et al. 2007).

In the EVLTAP study, SFJ occlusion was defined as flush occlusion of the GSV at the SFJ with any “knobbing” or stump no greater than 5 mm. Although GSV occlusion is more significant than SFJ occlusion following EVLT, we chose to monitor SFJ occlusion because of the possibility of developing reflux in the tributaries around the SFJ if it is not occluded or is incompetent. Most practitioners of EVLA would recommend commencing laser ablation about 1 – 2cm proximal (caudal) to the SFJ to prevent thrombus extension into the common femoral vein (Khilnani, Grassi et al. 2010). Using this technique of flush occlusion did not result in any definite case of thrombus extension into the

common femoral vein (CFV) in this series, or in the over 100 limbs treated up to the time of data collection, but not included in the EVLTAP series. We have had one case of a small eccentric thrombus in the CFV close to the SFJ, which was not contiguous with the non-thrombotic occlusion of the GSV. This may have been due to migration of the tip of the laser fibre during tumescent anaesthetic infiltration. It is pertinent to state however that we scanned our patients at 1, 6, and 12 weeks, whereas, earlier scanning (within 72 hours) appears to identify more cases of sub-clinical deep vein thromboses (Khilnani, Grassi et al. 2010).

At the 6 week follow up, three patients had thread veins that had become more prominent post laser ablation, while one patient had several small residual varices. None of these patients had duplex ultrasound scan evidence of treatment failure (non-occlusion or re-canalisation of the treated segment of vein). The patients with thread veins underwent successful treatment with liquid sclerotherapy. The single patient, who had residual varices, successfully underwent further ambulatory phlebectomy. These four limbs accounted for fewer than 6% of the 68 limbs seen at 6 weeks. This represents a vast reduction in the reported 30% - 99% of patients who require subsequent adjunctive procedures following EVLT only.

EVLTAP was associated with high levels of patient satisfaction with cosmetic appearance and overall treatment. Satisfaction was assessed in 2 areas to show that in addition to cosmetic outcome, patients were also satisfied with the whole EVLTAP procedure, and found it acceptable. Most previous studies have assessed patients' acceptance of EVLT in various ways, usually qualitatively,

and like our study, they have demonstrated an overwhelming acceptance of EVLT.

The EVLTAP study was a prospective observational series. When the results were first presented and published, the main criticism was that no comparison had been made with EVLA – only procedure. While this was accepted as a 'fair enough' criticism, it needed to be appreciated that this was a study to assess feasibility and acceptance of the modification of a new technique. As the results showed, although no direct comparison was made at that time, the concerns for patient discomfort, safe dose of anaesthetic and prolonged duration of the procedure, have not been borne out.

In summary, we have found the combined procedure of EVLTAP to be a feasible option, and an alternative to "EVLT only" procedure. EVLTAP is not unduly prolonged, and not associated with pain that may limit immediate return to normal activities. It is acceptable to patients, and vastly reduces the number of sequential treatments required. Since this study was completed, there have been several other reports of combining EVLA with phlebectomy, perforator surgery, foam sclerotherapy and high ligation (Florio, Del Papa et al. 2008, Kim, Kim et al. 2009, Christenson, Gueddi et al. 2010).

In 2007, EVLA was a relatively new treatment for varicose veins. The main aim of treatment for varicose veins is to improve QoL and prevent / treat complications. The benefit of any new treatment must be gauged against the current "gold standard", which in this case is surgery. Whilst current evidence

supporting EVLA for varicose veins provides acceptable GSV occlusion rates and patient acceptability, at that time, QoL outcomes were lacking. Successful treatment must take into account, patients' perception of benefit, assessed by QoL measures or satisfaction surveys (McDaniel, Nehler et al. 2000). We therefore designed a study to investigate not just clinical and technical outcomes, but especially QoL outcomes post EVLA. The prospective non randomised study was designed as a pilot study, to generate data which would be utilised in a planned randomised trial. At that time, that was the first study to analyze QoL outcomes following EVLA, and to compare these to the QoL outcomes following current gold standard treatment.

As this was a non-randomized trial, baseline intergroup differences were not unexpected. Analysis of co-variance, a technique that reduces bias in comparative studies, was performed to adjust for these baseline differences (Anderson, Auquier et al. 1980).

A significant decline in QoL was observed in the surgery group at 1-week post procedure. No such decline was observed following EVLA. Also, intergroup comparisons demonstrated significant QoL differences at the 1 and 6-week time points particularly in the physical SF36 domains. This suggests that the deleterious effects of surgery for varicose veins on patients' early QoL are not seen following EVLA. This is supported by EVLA case series, which have shown almost immediate return to normal activities. Thus the early physical benefits following minimally invasive EVLA are clear in comparison with surgery.

Many of the generic QoL scores in both groups improved significantly at 6 and 12 weeks. This demonstrates that the QoL benefits following varicose vein surgery are also seen following EVLA, with no difference at 12 weeks.

The disease-specific QoL analysis demonstrated some important variation in comparison with the generic QoL analysis. The decline in QoL at 1 week was statistically significant in both groups, whereas the decline in the SF-36 domain scores at 1 week following EVLA did not reach statistical significance. This difference is perhaps not unexpected. The AVVQ is a disease-specific instrument, and therefore generally accepted to be more responsive to change in varicose vein status. In addition, the AVVQ ascribes points for compression therapy. All patients in this study were advised to wear compression stockings for 6 weeks post intervention, potentially artificially increasing the AVVQ score. The routine prescription of pain relieving tablets may also have contributed to the increased AVVQ scores.

As seen in the SF-36 analysis, both groups experienced significant improvement in overall QoL following treatment for their disease. This adds to the body of evidence that varicose vein treatment improves patients' quality of life. It has to be said however, that the EVLA group experienced a higher AVVQ improvement at 12 weeks. This may indicate that as far as disease-specific QoL assessment is concerned, EVLA is better than surgery. However, the surgery group had higher AVVQ scores at baseline, and the difference between the groups at 12 weeks may represent residual venous insufficiency in this group, which had more symptomatic disease to begin with.

The improvement of our patients was not limited to QoL outcomes. As seen by the venous clinical severity scores, there was a significant improvement in the severity of our patients' disease. This improvement was similar at 12 weeks in both groups, and highlights the efficacy of both modalities of treatment. The majority of our patients in both groups had uncomplicated varicose veins (C2 CEAP classification), and specifically, none had active ulceration. However, in a series of 23 patients with varicose ulcers, EVLA without long-term compression resulted in ulcer healing in 22 patients, in a median time of 4 months (Sharif, Soong et al. 2006). There is therefore potential for EVLA to be effective in treating more severe disease.

The results must be interpreted in light of some limitations. Firstly is the fact that it was a non – randomised trial, and therefore subject to bias in terms of patient matching. This is a justified criticism; however the patient selection was based on previously detailed criteria, and no deliberate attempts were made to select the best patients for EVLA. Also, the patients were fairly well matched as can be seen from the baseline parameters, and during analysis of the results, an analysis of co-variance was performed to adjust for any baseline differences. It is however appreciated that this technique may not completely eliminate all bias. Another criticism was that the surgery cases were performed by different surgeons, including Specialist Registrars, while the EVLA cases were performed by a single consultant. Although it can be argued that there would be operator variability in the surgical cases, the fact was that all the surgeries were performed in a standard way, as practiced by the majority of vascular surgeons

in the UK, and the variability was minimal. Again, only about half of 62 patients in the surgery group had 12 week follow up. Whether or not this proportion was representative of the group can only be speculated upon.

In conclusion, this study highlighted firstly, both surgery and EVLA for varicose veins improve QoL, an important consideration for medical managers and policy makers during decision-making regarding resource allocation and service provision: varicose veins are not just a cosmetic problem. Secondly, in the early post intervention period, EVLA has a QoL advantage over surgery. Although this advantage becomes progressively reduced with time, it may have significant implications in terms of early return to normal lifestyle and activities. Even given this study's limitations, we believe it highlights important findings that need to be further investigated by a randomized clinical trial with prolonged follow up. In the period since this study was performed, our unit has gone on to investigate and compare QoL outcomes between surgery and EVLA in a randomised trial setting (Carradice, Mekako et al. 2011); The findings are similar. This confirms that EVLA definitely has QoL outcome advantages over standard surgery, especially in the early post intervention period.

Since the introduction, expansion of indications, and utilisation of minimally invasive therapies for varicose vein treatment, there has been a challenge to the concept of standard surgery being the gold standard treatment for varicose veins. However, at least for now, open varicose vein surgery, introduced by Babcock in the early 1900s, and modified over the years, remains the gold standard. Surgery is effective in eliminating varicosities, eradicating or

ameliorating symptoms, and restoring quality of life (MacKenzie, Paisley et al. 2002, Carradice, Mekako et al. 2011). When performed in a day case setting, it is also cost effective (Gohel, Epstein et al. 2010). Standard surgery however has important limitations. One such limitation is the fact that unlike the minimally invasive procedures which are usually performed under local anaesthetic in an office setting, surgery usually requires a general anaesthetic and an operating theatre. Although there are reports of performing groin dissection under local anaesthetic with or without sedation, and stripping the great saphenous vein under tumescent fluid infiltration (Rasmussen, Lawaetz et al. 2011), the standard practice is a general anaesthetic procedure.

Another limitation of surgery is the potential for wound problems, of which groin wound infection is most significant. Varicose vein surgery would be classified as clean surgery, and therefore have an estimated wound infection rate of 1 - 5% (Garner, Jarvis et al. 1988). Several series however, have variously reported higher rates of wound infection, reaching 16% in the series by Hayden and Holdsworth who investigated complications of groin re - exploration for recurrent varicose veins (Hayden and Holdsworth 2001). There is a likelihood that reported infection rates may reflect under representation, as currently, the vast majority of varicose vein operations are performed as day cases, with any wound infections manifesting in the community (Grogaard, Kimsas et al. 2001), often without the knowledge of the operating surgeon. When routine post - discharge surveillance is carried out, higher infection rates are reported. This fact was well highlighted by Avato and Lai who investigated the impact of post -

discharge surveillance on surgical site infection rates for coronary artery bypass procedures (Avato and Lai 2002). They found that only 28% of their total wound infections were diagnosed prior to discharge, with 78% manifesting in the community, after patients were discharged from hospital. The true rate of surgical site infections (SSIs) following varicose vein surgery is therefore not known.

Amongst surgical patients in the United Kingdom, surgical site infections are the commonest form of hospital acquired infection (Nosocmial Infection National Surveillance Service 2001). It is estimated that about 10% of patients in the UK, and 38% of patients in the USA experience SSIs each year (Mangram, Horan et al. 1999, Nosocmial Infection National Surveillance Service 2001). Prevention of SSIs depends to a large extent on critical factors such as surgical techniques and the general health and co morbidity of patients. However, the efficacy of prophylactic antibiotic use in reducing the risk of SSIs has long been demonstrated (Polk H C Jr and Lopez-Mayor J F 1969). In fact, it is estimated that 40% - 60% of SSIs are preventable by timely administered appropriate prophylactic antibiotics (Mangram AJ, Horan TC et al. 1999).

Surgical wound morbidity is not limited to infection, and many conventional definitions of SSI may be restrictive and not account for small, but significant patient – centred aspects of wound morbidity (Hall, Willsher et al. 2006). The use of wound scoring methods, of which the ASEPSIS is arguably the most widely used, in part overcomes this (Bruce, Russell et al. 2001).

Currently, there is disagreement among the several recognised definitions of SSIs, such that wounds that are classed as infected by one definition, may be classed as not infected by another (Wilson, Gibbons et al. 2004). The guideline from the Centres for Disease Control and Prevention (CDC) (Horan, Gaynes et al. 1992) for example, allows a definition of superficial SSI to be made on the basis of purulent drainage, while the ASEPSIS method defines infection as a total score of ≥ 21. In our study of antibiotic prophylaxis in varicose vein surgery, patients reported purulent discharge from 10.4% of wounds in the treatment group and 20.1% in the control group. If we defined wound infection using the ASEPSIS method, then 9.9% of the groin wounds in the treatment group and 18.2% of the control group would be classed as infected. These proportions satisfying both definitions are very similar, and show agreement between the ASEPSIS and CDC definitions in this trial; this would appear to validate our assessments and results. Whereas many ambulatory surgeons will claim low wound infection rates in clean surgery, the evidence in fact, is that many infections manifest in the community and are therefore undetected by the surgeon; these cannot be identified without adequate post-discharge wound surveillance (Reimer, Gleed et al. 1987, Weigelt, Dryer et al. 1992). Our results are in keeping with surveillance reports for clean wound SSI rates, and are not excessive.

With most infections manifesting post hospital discharge, community care practitioners (GPs and district nurses) take on the responsibility of managing these infections with consequential time and resource implications

(Perencevich, Sands et al. 2003). In our study, significantly more patients in the control group consulted their GPs for wound problems, and received antibiotics for perceived wound infections. Bjerrum et al have previously demonstrated that there is a degree of inappropriate antibiotic prescription by general practitioners, which is changed by education and training (Bjerrum, Cots et al. 2006). Even if it is argued that some antibiotic prescribing by GPs in our trial may have been inappropriate, it is pertinent however, that half of all patients who visited their GPs did not receive antibiotics. It is evident in our study, and worthy of note, that the use of prophylactic antibiotics resulted in significant reduction in the burden of postoperative wound management placed on primary care (evidenced by fewer visits to GPs, and fewer antibiotics prescribed).

The patient-dependent variables identified as predictors for poor wound outcome, namely high BMI and current cigarette smoking, are consistent with previous findings. (Sorensen, Horby et al. 2002, Itani, Wilson et al. 2006). We found female gender to be significantly associated with a good wound outcome in one multivariable model. This is contrary to the findings in Lichtenstein hernia repair (Aufenacker, van Geldere et al. 2004). However, in a study of antibiotic prophylaxis in patients undergoing elective colorectal surgery, male gender was significantly associated with the odds of a poor wound outcome (Itani, Wilson et al. 2006). Whether these findings are because men have a higher nasal carriage of S*taphylococcus aureus,* (Herwaldt, Cullen et al. 2004) or that hygiene is poorer in men, can only be speculative. Like others, we found that the administration of prophylactic antibiotic was an independent predictor of a

good wound outcome (Esposito, Leone et al. 2006, Itani, Wilson et al. 2006). Other studies have found significant associations between poor wound outcomes and age, (Bertin, Crowe et al. 1998) but our trial did not show this. We also did not find clinical class of varicose veins to have any association with poor wound outcomes. Antibiotic prophylaxis, high BMI and current smoking, remained significant independent variables associated with wound outcomes on patient-based modelling.

Due to the small number of patients with diabetes and those on steroids in our trial, these factors were not analysed for association with poor wound outcome. We also did not consider non-patient dependent variables (e.g. length of operation, surgeon's experience) which are recognised to be associated with poor wound outcomes. Day case provision for varicose vein surgery in our unit is consultant-led, with close supervision of higher surgical trainees. This results in minimal variability in experience and procedure duration.

The CDC stipulates a postoperative period of 30 days for making a definition of superficial SSI in non-implant wounds, and this has been used by many studies. However, about 90% of surgical wound infections manifest within three weeks post operatively, (Weigelt, Dryer et al. 1992) and in a study of antibiotic prophylaxis in clean groin surgery, all of the patients who developed SSI, did so in the first 7 days (Perez, Roxas et al. 2005). In our study, patients performed wound assessments up to the 10th postoperative day, and a blinded investigator reviewed all groin wounds at 14 days. We found a steady decline in reported wound problems, with the passage of time; such that on day 14, only a

relatively small proportion of patients had any wound problem. The deduction is that late onset wound morbidity would appear to be negligible. Therefore, although our period of observation was relatively short, we were likely to have detected the vast majority of patients with wound morbidity.

In investigating the effect of antibiotic prophylaxis in wound related complications post varicose vein surgery, this study used the ASEPSIS criteria for assessing wound problems. This method of scoring has been criticised as being over sensitive and may actually over call wound infection. This system however, is validated and is probably the most robust method of assessment. A criticism of the use of this system in this study would be the method of wound assessment. Whereas in the original design of the ASEPSIS wound assessment was carried out by healthcare personnel on an in-patient basis, it was necessary in this study to 'train' patients on self-assessment, due to the day – case nature of varicose vein surgery. This "limitation" has already been addressed in the discussion.

There are important highlights arising from this RCT. We have demonstrated that a significant proportion of patients undergoing surgery for varicose veins suffer groin wound morbidity. These problems usually manifest in the community and thus are managed by primary care providers, increasing pressures on time, manpower and resources. We have also demonstrated that the use of prophylactic antibiotics significantly reduced the wound morbidity, visit to a GP for postoperative wound problems, and the requirements for further antibiotics for postoperative wound infection. A high BMI and current smoking

are important patient-dependent factors significantly associated with a poor wound outcome. In light of these findings, we conclude that prophylactic antibiotics are beneficial in patients undergoing groin surgery for varicose veins, and should be routinely administered; especially if patients are obese and current smokers.

FUTURE PERSPECTIVES

There has been tremendous development in the area of varicose vein management since the time of the commencement of the studies contained in this thesis. During the initiation of these studies, 'the future' looked towards aspects such as ablation of small saphenous vein (SSV) varicosities, and of major tributaries such as anterolateral thigh veins (anterior accessory GSV). Also the future looked at comparing laser ablation with standard surgery in the setting of randomised trials. These are now the present, and in some respects, are now the 'past'. As has already been alluded to in the text, it is now routine to perform laser ablation for SSV and anterior accessory GSV varicosities.

Several units, including ours, have performed randomised comparisons of laser ablation with standard surgery. We found similar improvement in the venous clinical severity scores of patients, following treatment with both surgery and laser ablation. Of significance however, was that the quality of life impairment associated with standard surgery in the immediate and early post operative period, was absent with laser ablation (Carradice, Mekako et al. 2011), a finding which had already been noted in study 3 of this present work (Mekako, Hatfield et al. 2006). This led to earlier return to work and usual activities in patients undergoing laser ablation as compared to surgery.

Another advance that has occurred is in the utilisation of higher wavelength lasers. The studies in this thesis were performed using the 810nm diode laser. Higher wavelength lasers – 940nm, 980nm, 1320nm, 1470nm, and 1560nm –

have been trialled and now being utilised (Munavalli and Weiss 2006, Desmyttere, Grard et al. 2010, Pannier, Rabe et al. 2011). The lower wavelength lasers have affinity for haemoglobin and the absorption of heat by the haemoglobin in the red cells causes blood to boil, and the 'steam bubbles' thus generated, transfer energy to the vein wall. It is believed that the prolonged contact of these bubbles with the vein wall, as well as the direct effect of the heated laser fibre, results in vein wall perforation and charring, which contribute to the significant bruising and post procedural pain associated with the lower length lasers (Munavalli and Weiss 2006). The higher wavelength lasers have an affinity for water, and have been noted to cause up to 80% less bruising and pain than the lower wavelength fibres (Munavalli and Weiss 2006). There is however no unequivoval evidence to support superiority of any particular fibre wavelength.

The design of the laser fibres has also seen advances. The first laser fibres were bare-tipped, and these were utilised in the studies in this thesis. There have been developments aimed at reducing the vein wall contact by the laser tip, which was thought to cause charring and perforation of the vein wall, with resultant vein wall perforation and increased post procedure pain and bruising. Developments have seen the introduction of a 'jacket' to cover the bare tip (the jacket-tip fibre) as well as glass, ceramic, diffusion and radial fibres. These are thought to result in a more uniform transfer of energy to the vein wall, and therefore less vein wall perforation. Short term follow up has shown promise of less bruising, less pain, and equal efficacy with the bare-tip fibres (Doganci and

Demirkilic 2010), although some evidence of more treatment failures have been reported (Prince, Soares et al. 2011).

In November 2008, the CLASS (**C**omparison of **LA**ser, **S**urgery and foam **S**clerotherapy as a treatment for varicose veins) trial started recruitment. This is a multicentre randomised trial which compares minimally invasive treatment (laser and foam sclerotherapy) with surgery, with primary outcomes of clinical and cost effectiveness. The trial is ongoing, and the results are expected with anticipation, as it is hoped that un-biased answers will be provided.

The future perspectives from this point on, will be exploring long term outcomes with the use of higher wavelength fibres, lower energy delivery, newer designs of laser fibres, as well as cost effectiveness of EVLA as compared with other modalities of therapy – both conventional and minimally invasive.

IMPACT OF THIS WORK

The studies included in this thesis commenced in the early days of endovenous laser ablation of varicose veins. At the time, evidence was sparse and limited to a few case reports and case series, with no high level evidence directing practice.

The EVLTAP paper described a modification and adaptation of endovenous laser ablation. The paper won the second prize in the “poster of distinction” session of the Association of Surgeons of Great Britain and Ireland (ASGBI) annual conference in 2006. More importantly, it led to the design and performance of a randomised trial (Carradice, Mekako et al. 2009) by this unit and the adoption of EVLTAP practice by other units (Gloviczki, Comerota et al. 2011).

The non randomised trial of EVLA versus surgery study led on to the design and performance of several randomised trials which have contributed immensely to the literature.

Since the publication of the paper on antibiotic prophylaxis for varicose vein surgery, our unit has adopted the use of single dose antibiotic prophylaxis for varicose vein surgery. The adoption has seen a reduction of wound complications following varicose vein surgery (un - published in house audit).

In summary, the work contained in this thesis was fairly ground – breaking work at the time it was done. It formed the pilot data for future RCTs which were

performed within the Academic Vascular Unit in Hull, resulting in several prize presentations (Venous Forum, Vascular Society of Great Britain and Ireland) and led to papers published in high impact factor surgical journals. This resulting work contributed significantly (the largest published RCT of endovenous ablation verses surgery) to the body of evidence which has resulted in a huge sea of change in the way vascular surgeons manage superficial venous incompetence with generally >50% of cases being managed with an endovenous approach. Thus although now perhaps a little dated, the data presented in this thesis represents the foundations on which this huge change in clinical practice was based, and thus merits recognition.

SUMMARY AND CONCLUSION

The invasive treatment of lower limb varicose veins has evolved since Babcock first described a new way of extirpation of varicose veins of the Leg in 1907. Several developments and modifications of open surgery, including PIN stripping, cryostripping, etc, have made current day open surgery for varicose veins clinically effective, quite safe, and cost effective. It remains one of the most commonly performed surgical procedures in the developed world, and the "proven" gold standard as far as treatment of varicose veins is concerned.

Arguably the most significant development in varicose vein management came in the mid to late 1990s with the introduction of minimally invasive therapies in the form of endovenous thermal ablation. Of these techniques, endovenous laser ablation has undergone the greatest revolution and clinical application. EVLA mostly uses diode laser energy to cause thermal damage to the venous endothelium and subsequent non – thrombotic occlusion of the treated vein. It has proved to be as effective as, and possibly more effective than standard surgery, in terms of abolition of reflux and prevention of recurrent disease. Despite the enthusiasm that greeted the introduction of EVLA, and the desire to widen its application, in its early days, it was largely applied mainly to the treatment of reflux in the GSV. However, not all veins can be treated by EVLA, as some are anatomically unsuitable. When we performed our initial EVLA suitability study in 2005, using extremely tight criteria, only 56% of veins were found suitable. In the period since our feasibility study was carried out, the indications and utilisation of laser ablation have expanded tremendously. It is

now routine to perform laser ablation on small saphenous vein, anterior accessory GSV, recurrent varices, small calibre veins, and perforating veins. Very tortuous, small sized and superficial veins remain a challenge to the utility of EVLA.

The “standard” practice of EVLA is to perform truncal vein laser ablation only, and carry out any required tributary varicosity treatment subsequently. This means more than one treatment visit for most patients. This may be a relative “dissuasion” for patients, especially for those who need to take time off work. Study 2 of this work showed that it was both feasible and indeed acceptable to patients to combine EVLA with mini phlebectomy as a one - stage procedure. This practice (or a modification of it) has been taken up by several other practitioners in current day varicose vein management.

The monitoring of outcomes of the treatment of varicose veins has gone beyond technical and “clinical” success. Quality of life measures are now an integral part of outcome analyses. EVLA improves QoL in sufferers of varicose veins. This was clearly demonstrated in study 3: a non randomised controlled trial of EVLA and surgery in treatment of GSV varicosities. EVLA produced better QoL preservation and improvement especially in the early post intervention period, than did open surgery. This is an important effect, especially in the current economic climate, as it ensures earlier recovery and return to work following varicose vein treatment.

EVLA avoids the need for a groin incision and therefore eliminates the potential for a groin wound infection. Although varicose vein surgery is clean surgery, there remains a risk for surgical site infections and other wound complications. The use of prophylactic antibiotics has been shown in various settings to be effective in preventing or reducing the incidence of surgical site infections. Study 4 of this work looked specifically at this, in the setting of varicose vein surgery. The findings were clear and important: the use of prophylactic antibiotic significantly reduced wound complication, and the need to visit general practitioners and require antibiotics in the post operative period.

In the delivery of modern day surgical services, the trend towards less invasive interventions is clearly obvious. This is driven by patient, surgeon, and hospital management preferences, (possibly) imposed by the current economic climate. The hope (or assumption) is that the less invasive interventions would lead to a reduction in complications, length of hospital stay, and cost. The delivery of varicose vein services has towed the same line as the rest of surgery (and indeed Medicare). What is gratifying (and this is demonstrated in this work), is that EVLA as a frontline less invasive option, has fulfilled this hope. Although this present work did not include calculation of costs, other reports have shown that EVLA is cost effective. It therefore fulfils an ideal intervention for varicose veins, meeting important outcomes and qualities:

It is effective in abolishing reflux in the treated vein

It causes clinical improvement and eradication of symptoms

It is very safe, with few complications

It preserves and improves health related quality of life

It is cost effective

It is highly acceptable to patients

As already alluded to, not every patient or every varicose vein will be suitable for laser ablation; therefore surgery would still play an important role in management of varicose veins. The growth in the use of foam sclerotherapy (although not specifically studied in this work), means that there is yet another tool for the treatment of suitable veins and patients. There is as yet no one-cap-fits-all modality, and although almost any varicose vein can be treated by surgery, not all patients will want to have, (nor indeed can be candidates to have) open surgery. In spite of its current status as gold standard, it is inevitable that the role of standard surgery in the treatment of lower limb varicose vein will shrink significantly in the nearest future, in line with the expansion of minimally invasive techniques.

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Appendix 1: venous clinical severity score

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 VEINS[1]	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 OEDEMA[2]	None	Evening ankle oedema only	Afternoon oedema, above ankle	Morning oedema above ankle and requiring activity change, elevation
SKIN PIGMENTATION[3]	None or focal, low intensity (tan)	Diffuse, but limited in area and old (brown)	Diffuse over most of gaiter distribution (lower ⅓) *or* recent pigmentation (purple)	Wider distribution (above lower ⅓) *and* recent pigmentation
INFLAMMATION	None	Mild cellulitis, limited to marginal area around ulcer	Moderate cellulitis, involves most of gaiter area (lower ⅓)	Severe cellulitis (lower ⅓ and above) or significant venous eczema
INDURATION	None	Focal, circum-malleolar (<5cm)	Medial or lateral leg, less than lower ⅓ leg	Entire lower ⅓ leg or more
NO. OF ACTIVE ULCERS	0	1	2	>2
ACTIVE ULCERATION, DURATION	None	<3mths	>3mths, <1yr	Not healed >1yr
ACTIVE ULCER, SIZE[4]	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

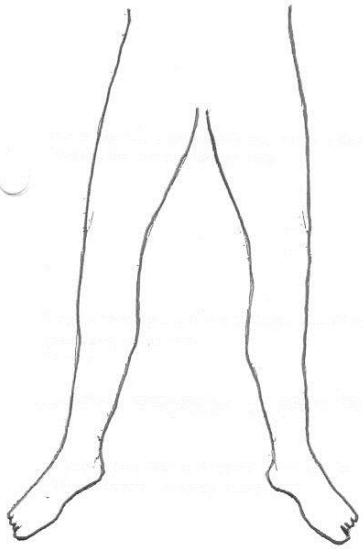
1. "Varicose" veins must be >4mm diameter to qualify so that differentiation is ensured between C1 and C2 venous pathology.
2. Presumed venous origin by characteristics (e.g. Brawny [not pitting or spongy] oedema), with significant effect of standing/limb elevation and/or other clinical evidence of venous 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.

Appendix 2: Aberdeen varicose vein questionnaire

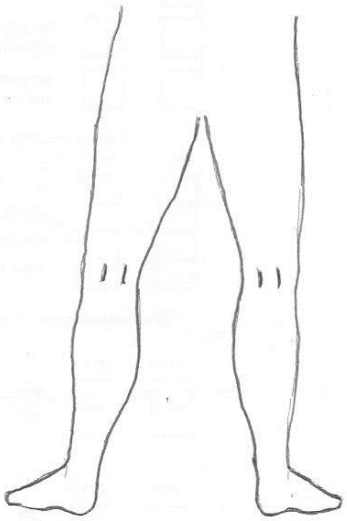
YOUR VARICOSE VEINS

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

Legs viewed from front



Legs viewed from back



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	☐	☐
Between 1 and 5 days	☐	☐
Between 6 and 10 days	☐	☐
For more than 10 days	☐	☐

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	☐
Between 1 and 5 days	☐
Between 6 and 10 days	☐
For more than 10 days	☐

4. In the last two weeks, how much ankle swelling have you had?
(Please tick one box)

None at all	☐
Slight ankle swelling	☐

Moderate ankle swelling (eg. causing you to sit with your feet up whenever possible) ☐

Severe ankle swelling (eg. causing you difficulty putting on your shoes) ☐

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	☐	☐
Yes, those I bought myself without a doctor's prescription	☐	☐
Yes, those my doctor prescribed for me which I wear occasionally	☐	☐
Yes, those my doctor prescribed for me which I wear every day	☐	☐

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	☐	☐
Yes, but only above the knee	☐	☐
Yes, but only below the knee	☐	☐
Both above and below the knee	☐	☐

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	☐	☐
Yes	☐	☐

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	☐	☐
Yes, but it does not require any treatment from a doctor or district nurse	☐	☐
Yes, and it requires treatment from my doctor or district nurse	☐	☐

9. Do you have a skin ulcer associated with your varicose veins?
(Please tick one box for each leg)

	R Leg	L Leg
No	☐	☐
Yes	☐	☐

10. Does the appearance of your varicose veins cause you concern?
(Please tick one box)

- No ☐
- Yes, their appearance causes me slight concern ☐
- Yes, their appearance causes me a great deal of concern ☐

11. Does the appearance of your varicose veins influence your choice of clothing including tights?
(Please tick one box)

- No ☐
- Occasionally ☐
- Often ☐
- Always ☐

12. During the last two weeks, have your varicose veins interfered with your work/ housework or other daily activities?
(Please tick one box)

- No ☐
- I have been able to work but my work has suffered to a slight extent ☐
- I have been able to work but my work has suffered to a moderate extent ☐
- My veins have prevented me from working one day or more ☐

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 ☐
- Yes, my enjoyment has suffered to a slight extent ☐
- Yes, my enjoyment has suffered to a moderate extent ☐
- Yes, my veins have prevented me taking part in any leisure activities ☐

Appendix 3: Short Form 36

Subject Initials :	___ ___ ___
Subject Number:	___ ___ – ___ ___ ___ ___
Date of Visit:	___ ___ – ___ ___ – 20 ___ ___ (dd mm yy)

SF-36 HEALTH SURVEY

INSTRUCTIONS: This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.

Answer every question by marking the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

1. In general, would you say your health is:

(circle one)

Excellent 1
Very good 2
Good 3
Fair 4
Poor 5

2. Compared to one year ago, how would you rate your health in general now?

(circle one)

Much better now than one year ago 1
Somewhat better now than one year ago 2
About the same as one year ago 3
Somewhat worse now than one year ago 4
Much worse now than one year ago 5

Subject Initials :	___ ___ ___
Subject Number:	___ ___ – ___ ___ ___
Date of Visit:	___ ___ – ___ ___ – 20 ___ ___ (dd mm yy)

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

(circle one number on each line)

ACTIVITIES	Yes, Limited A Lot	Yes, Limited A Little	No, Not Limited At All
a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	1	2	3
b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
c. Lifting or carrying groceries	1	2	3
d. Climbing several flights of stairs	1	2	3
e. Climbing one flight of stairs	1	2	3
f. Bending, kneeling, or stooping	1	2	3
g. Walking more than a mile	1	2	3
h. Walking half a mile	1	2	3
i. Walking one hundred yards	1	2	3
j. Bathing or dressing yourself	1	2	3

4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

(circle one number on each line)

	YES	NO
a. Cut down on the amount of time you spent on work or other activities	1	2
b. Accomplished less than you would like	1	2
c. Were limited in the kind of work or other activities	1	2
d. Had difficulty performing the work or other activities (for example, it took extra effort)	1	2

Subject Initials :	___ ___ ___
Subject Number:	___ ___ – ___ ___ ___ ___
Date of Visit:	___ ___ – ___ ___ – 20 ___ ___ dd mm yy

5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

(circle one number on each line)

	YES	NO
a. Cut down on the amount of time you spent on work or other activities	1	2
b. Accomplished less than you would like	1	2
c. Didn't do work or other activities as carefully as usual	1	2

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?

(circle one)

Not at all 1
Slightly 2
Moderately 3
Quite a bit 4
Extremely 5

7. How much bodily pain have you had during the past 4 weeks?

(circle one)

None 1
Very mild 2
Mild 3
Moderate 4
Severe 5
Very severe 6

Subject Initials :	___ ___ ___
Subject Number:	___ ___ – ___ ___ ___
Date of Visit:	___ ___ – ___ ___ – 20 ___ ___ dd mm yy

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

(circle one)

Not at all 1

A little bit 2

Moderately 3

Quite a bit 4

Extremely 5

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks -

(circle one number on each line)

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
a. Did you feel full of life?	1	2	3	4	5	6
b. Have you been a very nervous person?	1	2	3	4	5	6
c. Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
d. Have you felt calm and peaceful?	1	2	3	4	5	6
e. Did you have a lot of energy?	1	2	3	4	5	6
f. Have you felt downhearted and low?	1	2	3	4	5	6
g. Did you feel worn out?	1	2	3	4	5	6
h. Have you been a happy person?	1	2	3	4	5	6
i. Did you feel tired?	1	2	3	4	5	6

Subject Initials :	___ ___ ___
Subject Number:	___ ___ – ___ ___ ___
Date of Visit:	___ ___ – ___ ___ – 20 ___ ___ dd mm yy

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

(circle one)

All of the time 1

Most of the time 2

Some of the time 3

A little of the time 4

None of the time 5

11. How TRUE or FALSE is each of the following statements for you?

(circle one number on each line)

	Definitely True	Mostly True	Don't Know	Mostly False	Definitely False
a. I seem to get ill more easily than other people	1	2	3	4	5
b. I am as healthy as anybody I know	1	2	3	4	5
c. I expect my health to get worse	1	2	3	4	5
d. My health is excellent	1	2	3	4	5