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[Intervention Review]

Subfascial endoscopic perforator surgery (SEPS) for treating venous leg ulcers

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ABSTRACT

Background

Venous leg ulcers are complex, costly, and their prevalence is expected to increase as populations age. Venous congestion is a possible cause of venous leg ulcers, which subfascial endoscopic perforator surgery (SEPS) attempts to address by removing the connection between deep and superficial veins (perforator veins). The effectiveness of SEPS in the treatment of venous leg ulcers, however, is unclear.

Objectives

To assess the benefits and harms of subfascial endoscopic perforator surgery (SEPS) for the treatment of venous leg ulcers.

Search methods

In March 2018 we searched the Cochrane Wounds Specialised Register; the Cochrane Central Register of Controlled Trials (CENTRAL); Ovid MEDLINE (including In-Process & Other Non-Indexed Citations); Ovid Embase and EBSCO CINAHL Plus. We also searched clinical trials registries for ongoing and unpublished studies, and scanned reference lists of included studies as well as reviews, meta-analyses and health technology reports to identify additional studies. There were no restrictions with respect to language, date of publication or study setting.

Selection criteria

We included randomised controlled trials (RCTs) of interventions that examined the use of SEPS independently or in combination with another intervention for the treatment of venous leg ulcers.

Data collection and analysis

Two review authors independently selected studies for inclusion, extracted data, assessed risk of bias, and assessed the certainty of evidence using the GRADE approach.

Main results

We included four RCTs with a total of 322 participants. There were three different comparators: SEPS plus compression therapy versus compression therapy (two trials); SEPS versus the Linton procedure (a type of open surgery) (one trial); and SEPS plus saphenous surgery versus saphenous surgery (one trial). The age range of participants was 30 to 82, with an equal spread of male and female participants. All trials were conducted in hospital settings with varying durations of follow-up, from 18 months to 6 years. One trial included participants who had both healed and active ulcers, with the rest including only participants with active ulcers.

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There was the potential for reporting bias in all trials and performance bias and detection bias in three trials. Participants in the fourth trial received one of two surgical procedures, and this study was at low risk of performance bias and detection bias.

SEPS + compression therapy versus compression therapy (2 studies; 208 participants)

There may be an increase in the proportion of healed ulcers at 24 months in people treated with SEPS and compression therapy compared with compression therapy alone (risk ratio (RR) 1.17, 95% confidence interval (CI) 1.03 to 1.33; 1 study; 196 participants); low-certainty evidence (downgraded twice, once for risk of bias and once for imprecision).

It is uncertain whether SEPS reduces the risk of ulcer recurrence at 24 months (RR 0.85, 95% CI 0.26 to 2.76; 2 studies; 208 participants); very low-certainty evidence (downgraded three times, twice for very serious imprecision and once for risk of bias).

The included trials did not measure or report the following outcomes; time to complete healing, health-related quality of life (HRQOL), adverse events, pain, duration of hospitalisation, and district nursing care requirements.

SEPS versus Linton approach (1 study; 39 participants)

It is uncertain whether there is a difference in ulcer healing at 24 months between participants treated with SEPS and those treated with the Linton procedure (RR 0.95, 95% CI 0.83 to 1.09; 1 study; 39 participants); very low-certainty evidence (downgraded three times, twice for very serious imprecision and once for risk of bias).

It is also uncertain whether there is a difference in risk of recurrence at 60 months: (RR 0.47, 95% CI 0.10 to 2.30; 1 study; 39 participants); very low-certainty evidence (downgraded three times, twice for very serious imprecision and once for risk of bias).

The Linton procedure is possibly associated with more adverse events than SEPS (RR 0.04, 95% CI 0.00 to 0.60; 1 study; 39 participants); very low-certainty evidence (downgraded three times, twice for very serious imprecision and once for risk of bias).

The outcomes time to complete healing, HRQOL, pain, duration of hospitalisation and district nursing care requirements were either not measured, reported or data were not available for analysis.

SEPS + saphenous surgery versus saphenous surgery (1 study; 75 participants)

It is uncertain whether there is a difference in ulcer healing at 12 months between participants treated with SEPS and saphenous surgery versus those treated with saphenous surgery alone (RR 0.96, 95% CI 0.64 to 1.43; 1 study; 22 participants); very low certainty evidence (downgraded three times, twice for very serious imprecision and once for high risk of reporting bias).

It is also uncertain whether there is a difference in the risk of recurrence at 12 months: (RR 1.03, 95% CI 0.15 to 6.91; 1 study; 75 participants); very low certainty evidence (downgraded three times, twice for very serious imprecision and once for high risk of reporting bias).

Finally, we are uncertain whether there is an increase in adverse events in the SEPS group (RR 2.05, 95% CI 0.86 to 4.90; 1 study; 75 participants); very low certainty evidence (downgraded three times, twice for very serious imprecision and once for high risk of reporting bias).

The outcomes time to complete healing, HRQOL, serious adverse events, pain, duration of hospitalisation, and district nursing care requirements were either not measured, reported or data were not available for analysis.

Authors' conclusions

The role of SEPS for the treatment of venous leg ulcers remains uncertain. Only low or very low-certainty evidence was available for inclusion. Due to small sample sizes and risk of bias in the included studies, we were unable to determine the potential benefits and harms of SEPS for this purpose. Only four studies met our inclusion criteria, three were very small, and one was poorly reported. Further high-quality studies addressing the use of SEPS in venous leg ulcer management are likely to change the conclusions of this review.

PLAIN LANGUAGE SUMMARY

Does subfascial endoscopic perforator surgery (leg-vein surgery) help heal venous leg ulcers?

What is the aim of this review?

Subfascial endoscopic perforator surgery (SEPS) involves cutting and closing off damaged perforator veins (blood vessels that link superficial and deep veins) in the leg. The aim of this review was to find out whether SEPS can help heal venous leg ulcers (slow-healing skin wounds caused by poor blood flow through leg veins). We collected and analysed all relevant randomised controlled trials (a type of study in which participants are assigned to one of two or more treatment groups using a random method, which provides the most reliable evidence) to answer this question and identified four studies for inclusion.

Key messages

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It is uncertain whether SEPS is beneficial or safe as a treatment for venous leg ulcers, as the certainty of the evidence collected is low or very low, and the included studies involved small numbers of participants.

What was studied in the review?

Venous leg ulcers are a common and costly health problem. These chronic wounds often take months to heal and have a high chance of recurrence after healing. Venous leg ulcers can be caused by veins that do not work properly, which results in blood flowing in the wrong direction between the superficial and deep veins in the leg. Blood that does not flow correctly causes increased pressure and inflammation, leading to skin breakdown and ulceration in the lower leg. Subfascial endoscopic perforator surgery can prevent blood from flowing in the wrong direction by cutting and tying veins that link the superficial and deep veins. It is unclear if SEPS is more effective than other treatment options such as compression bandages or stockings, which are the standard treatment for venous leg ulcers. We therefore investigated if this surgical technique can help venous leg ulcers heal more quickly. We also considered whether the surgery had any side effects, and if it impacted study participants' quality of life, experience of pain, or time spent in hospital and nursing care.

What are the main results of the review?

We included four studies in the review which dated from 1997 to 2011 and compared SEPS with other treatments for venous leg ulcers. The studies involved a total of 322 participants, ranging in age from 30 to 82 years, with an equal number of males and females.

Two studies compared SEPS and compression stockings with compression alone; one study compared SEPS against the Linton surgical procedure (a type of open surgery on leg veins); and one study compared SEPS in addition to saphenous vein surgery (surgery on the largest superficial vein in the leg) versus saphenous vein surgery alone.

We concluded that the evidence is insufficient to determine if SEPS results in better, worse, or the same outcomes as compression treatment in terms of ulcer healing. There may be a benefit of SEPS in terms of proportion of ulcers healed at 24 months, however evidence for this is of low certainty. It is also unclear due to the very low certainty of the evidence if SEPS as an addition to saphenous surgery, or as compared to the Linton approach, makes any difference in venous leg ulcer healing. No studies reported on quality of life, serious side effects or home nursing care requirements for study participants.

All four studies were small in size, with the largest including 200 participants, and the other three studies reporting on 75 participants or fewer. This factor, along with poor study design methods, means that the evidence about the role of SEPS in treating venous leg ulcers is of low or very low certainty. It therefore remains unclear whether SEPS is beneficial or safe in venous leg ulcer treatment, and further high-quality studies with larger sample sizes are likely to change the conclusions of this review.

How up-to-date is this review?

We searched for all studies published up to March 2018.

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SUMMARY OF FINDINGS

Summary of findings for the main comparison. Subfascial endoscopic perforator vein surgery (SEPS) + compression versus compression alone for treating venous leg ulcers

Subfascial endoscopic perforator vein surgery (SEPS) + compression compared to compression alone for treating venous leg ulcers

Patient or population: participants with venous leg ulcers
Setting: hospital - multicentre
Intervention: SEPS + standard compression therapy
Comparison: compression therapy

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with compression	Risk with SEPS + compression				
Proportion with ulcers healed at 24 months	765 per 1000	895 per 1000 (788 to 1000)	RR 1.17 (1.03 to 1.33)	196 (1 RCT)	⊕⊕⊝⊝ Low[1]	There is low-certainty evidence that SEPS may increase the proportion of ulcers healed. Anticipated absolute effects: if 76.5% experienced healing with compression, 89.5% will do so after SEPS + compression (2.3% to 25.2% more)
Time to complete healing	See comment					Not reported in any studies
Ulcer recurrence at 24 months	222 per 1000	189 per 1000 (58 to 613)	RR 0.85 (0.26 to 2.76)	208 (2 RCTs)	⊕⊝⊝⊝ Very low[2]	We are uncertain if there is a difference between groups as the estimate is imprecise with wide confidence intervals.
Quality of life	See comment					Not measured in any studies
Adverse events	See comment					Not reported in any studies
Pain	See comment					Not measured in any studies

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[1]Downgraded twice: once for more than two domains at unclear risk of bias, and once for imprecision due to small sample size.
[2]Downgraded three times: once for more than two domains at unclear risk of bias, and twice for very serious imprecision due to small sample size and wide confidence interval.

Summary of findings 2. Subfascial endoscopic perforator vein surgery (SEPS) compared to the Linton procedure for treating venous leg ulcers

Subfascial endoscopic perforator vein surgery (SEPS) compared to the Linton procedure for treating venous leg ulcers

Patient or population: participants with venous leg ulcers
Setting: hospital - multicentre
Intervention: SEPS
Comparison: Linton procedure

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Linton procedure	Risk with SEPS				
Proportion of ulcers healed at 24 months	1000 per 1000	950 per 1000 (830 to 1000)	RR 0.95 (0.83 to 1.09)	39 (1 RCT)	⊕⊖⊖⊖ Very low[1]	We are uncertain if there is a difference between groups. The estimate of the 95% CI of RR includes 1.
Time to complete healing	See comments					Not measured in any studies
Ulcer recurrence at 60 months	211 per 1000	99 per 1000 (21 to 484)	RR 0.47 (0.10 to 2.30)	39 (1 RCT)	⊕⊖⊖⊖ Very low[1]	We are uncertain if there is a difference between groups. The estimate is imprecise, with the 95% CI of RR including 1 and wide confidence intervals.
Quality of life	See comments					Not measured in any studies
Adverse events[2]	632 per 1000	25 per 1000 (0 to 379)	RR 0.04 (0.00 to 0.60)	39 (1 RCT)	⊕⊖⊖⊖ Very low[1]	We are uncertain if there is an increase in adverse events in the Linton group. Anticipated absolute effects: if 63.2% of participants experienced adverse events after the Linton procedure, 0% will do so after SEPS (63.2% less).

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Pain	See comments	Not measured in any studies

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[1]Downgraded three times: once for more than two domains at unclear risk of bias, and twice for very serious imprecision due to small sample size.
[2]Note that the trial was stopped early due to a higher wound infection rate in participants in the Linton group.

Summary of findings 3. Subfascial endoscopic perforator vein surgery (SEPS) + saphenous surgery compared to saphenous surgery for treating venous leg ulcers

Subfascial endoscopic perforator vein surgery (SEPS) + saphenous surgery compared to saphenous surgery for treating venous leg ulcers

Patient or population: participants with venous leg ulcers
Setting: hospital - multicentre
Intervention: SEPS + saphenous surgery
Comparison: saphenous surgery

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with saphenous surgery	Risk with SEPS + saphenous surgery				
Proportion of ulcers healed at 12 months	833 per 1000	800 per 1000 (533 to 1000)	RR 0.96 (0.64 to 1.43)	22 (1 RCT)	⊕⊖⊖⊖ Very low[1]	We are uncertain if there is a difference between groups. The estimate is imprecise, with the 95% CI of RR including 1 and wide confidence intervals.
Time to complete healing	See comments					Not clearly reported in any studies; it was unclear if all participants experienced healing during the trial period.

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Ulcer recurrence at 12 months	53 per 1000	54 per 1000 (8 to 364)	RR 1.03 (0.15 to 6.91)	75 (1 RCT)	⊕⊖⊖⊖ Very low[1]	We are uncertain if there is a difference between groups. The estimate is imprecise, with the 95% CI of RR including 1 and wide confidence intervals.
Quality of life	See comments					Not measured in any studies
Adverse events	158 per 1000	324 per 1000 (136 to 774)	RR 2.05 (0.86 to 4.90)	75 (1 RCT)	⊕⊖⊖⊖ Very low[1]	We are uncertain if there is a difference between groups. The estimate is imprecise, with the 95% CI of RR including 1 and wide confidence intervals.
Pain	See comments					Not measured in any studies

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[1]Downgraded three times: once for high risk of reporting bias, and twice for very serious imprecision due to small sample size and wide confidence interval.

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BACKGROUND

Description of the condition

Chronic venous leg ulcers are open wounds that have been present for at least four weeks, and can become infected (Bergan 2002). They are usually located in the lower limb region, between the malleolus and calf muscle, and most involve the medial aspect of the leg (De Souza 2013). Venous leg ulcers are a common problem and a significant burden on the individual and on healthcare systems. The underlying reasons for leg ulcer formation are broadly categorised into arterial, venous, diabetic, or mixed pathologies (Baker 1992; Chen 2007). Venous leg ulcers are the most common type, responsible for nearly 70% of chronic lower limb ulcers (Abbade 2005), and are the focus of this review. They occur spontaneously or after minor trauma and are often painful and associated with heavy amounts of wound discharge. Risk factors for venous leg ulcer development include increasing age, obesity, immobility, varicose veins, previous trauma, surgery, or deep vein thrombosis (Alguire 1997).

The pathophysiology underlying venous leg ulcer formation involves damage to deep or superficial leg veins, resulting in venous incompetence or insufficiency. Venous incompetence leads to high venous pressures, which can cause leakage of damaging inflammatory material from capillaries that results in fibrosis of surrounding skin and subcutaneous tissue (Abbade 2005). Poor nutrition and ischaemia of the area cause tissue breakdown and impede healing, which may lead to ulcers (Patel 2006).

Venous leg ulcers are often slow to heal, and up to 50% of new ulcers reoccur, as the natural history of ulceration is a cycle of healing and recurrence (Abbade 2005; Donnelly 2009; Moffatt 2007). The chronic and relapsing pattern of this condition has been shown to negatively affect an individual's quality of life, work productivity, and self esteem (De Araujo 2003; Persoon 2004; Productivity Commission 2005). Associated healthcare costs and required caring time also impact substantially on carers and the wider health service (Vowden 2006).

Compression therapy to improve venous return is the current best-practice treatment (O'Meara 2012), however between 30% to 50% of venous leg ulcers remain unhealed after two years (Weller 2013b). Various surgical procedures that aim to address the chronic venous insufficiency underlying venous leg ulcer formation have therefore been applied as adjunctive therapy. Subfascial endoscopic perforator surgery (SEPS) is a minimally invasive surgery used to treat chronic venous insufficiency and venous leg ulcers (Luebke 2009). There is little consensus, however, on the relative benefits of this surgery for treating venous leg ulcers (AWMA 2011; O'Donnell 2014; SIGN 2010).

Epidemiology of venous leg ulcers

Chronic venous insufficiency prevalence ranges from 1% to 40% in females and 1% to 17% in males, varying across location and population risk factors (Beebe-Dimmer 2005). Venous ulceration is a known complication of chronic venous insufficiency affecting up to almost 0.3% of the general adult population at any one time (O'Donnell 2014; Rice 2014). There is also increased prevalence in people over the age of 60 resulting in age-related venous leg ulcers becoming the most common cause of lower limb ulceration in the Western world (Baker 1991; Hess 2011; Margolis 2002; Passman 2010; Robertson 2008).

In Australia, the annual cost of venous leg ulcers increased from AUD 400 million in 1994 to AUD 3 billion a decade later (Angel 2005; Baker 1994). Similarly in the USA, the cost of treating venous leg ulcers rose from an estimated USD 1 billion in the early 1990s to USD 14.9 billion in 2011 (Olin 1999; Rice 2014). In the UK, the annual cost is estimated to range from GBP 300 million to GBP 600 million (USD 436 million to USD 872 million) per year (Soares 2009). Individual costs have been reported to range from hundreds to thousands of dollars per year, and this does not account for intangible costs such as loss of productivity for the patient or their carer, or both (AWMA 2011; Price 2000; Rice 2014; Stacey 2001). Total venous leg ulcer-associated costs may approach as much as 1% of the healthcare budget of Western countries (O'Donnell 2011).

Current treatments for venous leg ulcers

Venous leg ulcers may be treated conservatively, with compression bandaging and wound care (Nelson 2014; O'Meara 2012; Weller 2013a), medically, surgically, or with a combination of approaches, depending on the severity of the ulcer and available resources (Khan 2012; Tassiopoulos 2000). Firm compression bandaging to reduce venous hypertension and enhance venous return is the first line treatment (Grey 2006; Iglesias 2004; Nelson 2014; O'Meara 2012), however this strategy has only moderate effects on healing (Weller 2013b). Guidelines from Australia and New Zealand, the UK, and North America agree that routine care must include conservative wound dressing with compression therapy; however, referral to a vascular surgeon is also recommended to consider options for preventing recurrence (AWMA 2011; O'Donnell 2014; SIGN 2010). These more invasive procedures involve removing or repairing the veins surgically. Other adjunct strategies include physical therapy, systemic drug treatments, and home- or community-based management (Hafner 1999; Lurie 2003; McDaniel 2002; Nelson 2014; O'Meara 2012; Weller 2013b; Wollina 2006).

Prior to 2018, there was insufficient evidence to determine the role of venous surgery, or to recommend one surgical method over another for venous leg ulcers (AWMA 2011; Goel 2015; O'Donnell 2014; SIGN 2010). However, a recently published randomised controlled trial suggests benefit of early endovascular ablation compared with deferred endovascular ablation for those with venous leg ulcers in terms of reduced time to healing and more time free from ulcers (Gohel 2018). Historically, several surgical treatment options have been used in the management of venous leg ulcers, including SEPS, venous ligation and stripping (tying off or removing damaged veins), ambulatory phlebectomy (a minimally invasive outpatient procedure to remove superficial veins), vein bypass and reconstruction, endovenous thermal ablation (closure of veins with heat treatment using laser or radio waves), transluminal occlusion of perforators (inserting a needle into smaller blood vessels to close off damaged veins), and sclerotherapy ablation (injecting a substance such as foam into a damaged vein to close it off) (Bacon 2009; Goel 2015; Tenbrook 2004). However, the relative benefit or indications for use of these treatments remain to be definitively shown.

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Description of the intervention

Subfascial endoscopic perforator surgery (SEPS) is a minimally invasive procedure in which the perforator veins in the lower leg are cut and clamped to prevent blood flow through them (Bergan 2002). The aim of SEPS is to eliminate the major cause of venous leg ulcers, chronic venous insufficiency, and may therefore prove to be an efficacious treatment. In addition, by removing the underlying cause of venous insufficiency, SEPS may be a method of inhibiting the cycle of recurrence that is commonly associated with venous leg ulcers. SEPS involves small incisions being made in the upper calf above the ulcer site through which endoscopic surgical instruments access the veins. SEPS is a less invasive technique than open surgical procedures such as venous stripping, great saphenous vein surgery, and the Linton surgical procedure (in which a long medial calf incision is used to expose perforator veins) (Bergan 2002; Goel 2015; Lang 2001). SEPS can be carried out under sedation or local or general anaesthesia. SEPS carries the same risks inherent in all operations including bleeding, pain, infection, and damage to surrounding structures.

How the intervention might work

The superficial veins of the leg drain directly to the iliac veins or through deep fascia into the deep veins of the leg via the perforator veins (Padberg 2001). If venous incompetence occurs within these perforator veins, there will be a backflow of blood into the superficial venous system, leading to venous hypertension and, potentially, a venous leg ulcer (Burnand 2001). Surgical management of venous incompetence using the SEPS approach is thus proposed to improve venous leg ulcer healing rates and prevent ulcer recurrence (Bergan 2002).

Why it is important to do this review

As a less invasive technique compared with open procedures, SEPS has the potential benefit of reducing surgical wound-healing times and the aforementioned surgical complications including sepsis. However, there is conflicting evidence as to the benefit of SEPS in the management of venous leg ulcers (AWMA 2011). Reasons for this include varying study endpoints, such as time taken for the ulcer to heal, or a focus on complications of deep vein incompetence other than venous leg ulcers (Mauck 2014).

Previous reviews report conflicting findings with regard to the effects of SEPS for the treatment of venous leg ulcers (Luebke 2009; Mauck 2014; Tenbrook 2004). A non-Cochrane Review published in 2009 suggested SEPS was advantageous when compared with the Linton surgical procedure in the treatment of chronic venous insufficiency and the prevention of venous leg ulcer recurrence, but the effect of SEPS on venous ulcer healing remained unclear (Luebke 2009). Another review assessed the utility of SEPS for treating chronic venous insufficiency, the underlying pathophysiology of venous leg ulcers, but did not address the question of SEPS for venous leg ulcer treatment specifically (Tenbrook 2004). Results from that review should be interpreted with caution due to the limited search strategy and possibly inappropriate pooling of disparate study designs. The Australian Wound Management Association and New Zealand Wound Care Society also acknowledge that definitive evidence on surgical management of venous leg ulcers is lacking, and hence omit this topic from their guidelines (AWMA 2011).

There is no Cochrane Review of SEPS for the treatment of venous leg ulcers. This review is in the context of SEPS as a stand-alone surgery compared with other surgeries, or as an adjunctive therapy; for example, SEPS with conservative management versus conservative management alone, or SEPS with saphenous surgery versus saphenous surgery alone. Current practice accepts that compression bandaging is an important contributor to the healing of venous leg ulcers, therefore we expect that this will be included for all participants in all trials.

Given the potential benefit of SEPS as a minimally invasive surgical option that may improve outcomes in this debilitating and costly chronic condition, thorough appraisal of the literature is warranted. In this systematic review we have synthesised the currently available evidence and have assessed the relative benefits and safety of SEPS for venous leg ulcer treatment.

OBJECTIVES

To assess the benefits and harms of subfascial endoscopic perforator surgery (SEPS) for the treatment of venous leg ulcers.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) reported as full text, abstract only, or unpublished data. There was no language restriction.

Types of participants

We included studies in which participants were adults with venous leg ulcers, defined as ulcers in the lower leg or ankle due to underlying venous disease. We also included participants with venous leg ulcers that may have been complicated by other comorbidities such as diabetes. The rationale for this was to provide a result more representative of real-patient population demographics, and ideally increase the generalisability of our review findings. We excluded participants with leg ulcers caused by other aetiologies unrelated to venous ulcers, such as arterial, diabetic, or mixed aetiologies. We included studies with mixed populations provided that separate data were available for participants with venous leg ulcers.

Types of interventions

The intervention was subfascial endoscopic perforator surgery (SEPS), either alone or in combination with another treatment method.

We accepted surgical and non-surgical comparators, including but not limited to the following:

- conservative management alone (defined as compression bandaging or general wound care, or both);
- sham surgery (defined as a surgery that mimics the outward wound appearance of SEPS);
- another surgery for venous leg ulcer management that does not utilise SEPS (e.g. saphenous surgery, venous stripping);
- SEPS in conjunction with another surgical intervention (this was only accepted if the additional treatment method was applied

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to both intervention and comparator groups, that is as a co-intervention in both groups);
- an alternative active intervention (e.g. debridement, zinc, mesoglycan, nutritional supplements, electromagnetic therapy, therapeutic ultrasound, topical agents).

It was expected that all treatment groups would have received compression bandaging, given that this is widely recognised as routine care for venous leg ulcers (Nelson 2014).

We excluded studies where SEPS in combination with another intervention was compared with a third intervention (e.g. SEPS + saphenous surgery versus conservative management), as the effects of SEPS could not be isolated.

Types of outcome measures

We did not limit study inclusion based on reporting of outcome measures.

Primary outcomes

- Venous ulcer healing (i.e. proportion of ulcers healed within trial period, as defined by the trial authors).
- Time to complete healing (i.e. time from treatment commencement until ulcer resolution).
- Recurrence of venous ulcer (as reported in the trial).

Secondary outcomes

- Health-related quality of life (HRQOL), e.g. modified Skindex, Hareendran 2005, or common measures such as the 36-item Short Form Health Survey (SF- 36), EQ-5D.
- Adverse events (proportion of participants with any adverse event as defined by the individual trial).
- Serious adverse events (defined as an event resulting in hospitalisation, prolongation of hospitalisation, persistent or significant disability, a life-threatening event, or death).
- Pain (as a continuous outcome, e.g. mean pain or mean change in pain, measured by visual analogue scale, numerical or categorical rating scale; or as a dichotomous outcome, e.g. proportion of participants reporting complete pain relief or proportion reporting at least 50% improvement in pain relief). No trials examined pain as an outcome measure, however we intended to also include one or more other measures of pain for the purpose of pooling data. We intended to combine overall pain with other types of pain in the following hierarchy: unspecified pain; pain at night; pain with activity; or daytime pain.
- Duration of hospitalisation.
- District nursing care requirements.

We had planned to extract data at 6, 12, and 24 month time points. We had originally planned to only present 24 month data in the 'Summary of findings' tables. However, two studies only measured ulcer recurrence rate at other time points, (18 months - Callini 2002), (60 months - Pierik 1997), so rather than exclude these data, we included these time points in our analyses. See Differences between protocol and review'. For adverse events, we only extracted the last time point.

Search methods for identification of studies

Electronic searches

We searched the following electronic databases to identify reports of relevant clinical trials:

- the Cochrane Wounds Specialised Register (searched 4 March 2018);
- the Cochrane Central Register of Controlled Trials (CENTRAL; 2018, Issue 2) in the Cochrane Library (searched 4 March 2018);
- Ovid MEDLINE (including In-Process & Other Non-Indexed Citations (1946 to 4 March 2018);
- Ovid Embase (1974 to 4 March 2018);
- EBSCO CINAHL Plus (Cumulative Index to Nursing and Allied Health Literature) (1937 to 4 March 2018).

The search strategies for the Cochrane Wounds Specialised Register, CENTRAL, Ovid MEDLINE, Ovid Embase, and EBSCO CINAHL Plus can be found in Appendix 1. We combined the Ovid MEDLINE search with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximising version (2008 revision) (Lefebvre 2011). We combined the Embase search with the Ovid Embase filter developed by the UK Cochrane Centre (Lefebvre 2011). We combined the CINAHL Plus searches with the trial filters developed by the Scottish Intercollegiate Guidelines Network (SIGN 2018). We did not restrict studies with respect to language or date of publication.

We also searched the following clinical trials registries:

- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov/) (searched 4 March 2018);
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/Default.aspx) (searched 4 March 2018);
- EU Clinical Trials Register (www.clinicaltrialsregister.eu/) (searched 4 March 2018).

Search strategies for clinical trial registries can be found in Appendix 1.

Searching other resources

We checked the reference lists of all relevant publications identified by the database searches for additional eligible studies.

Data collection and analysis

We carried out data collection and analysis according to the methods stated in the published protocol (Lin 2016), which were based on the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011c).

Selection of studies

Two review authors (ZCL, PL) independently assessed the titles and abstracts of all studies identified by the search and excluded any clearly irrelevant studies. Full-text copies of potentially eligible studies were obtained and reviewed using the inclusion criteria. Any disagreements about inclusion were resolved by consensus or by consulting a third review author (RJ, MB, or CW) when

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necessary. The study selection process is summarised in a PRISMA flow diagram in Figure 1 (PRISMA 2009). See the Characteristics of excluded studies table for details of studies excluded after full-text review. See the Characteristics of included studies table for details of included studies. We identified no ongoing studies or studies awaiting classification.

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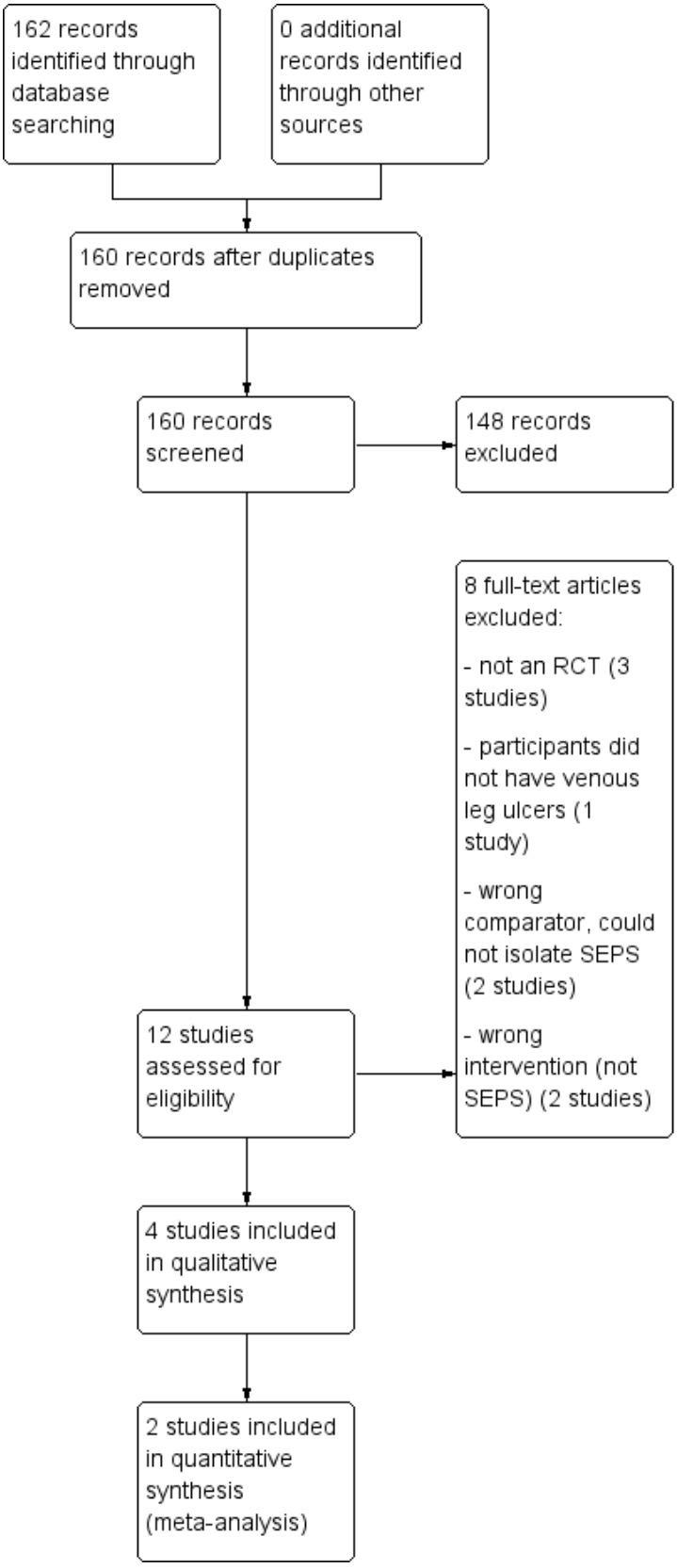
Figure 1. PRISMA flow chart Study flow diagram of the number of records identified, included, and excluded, and the reasons for exclusions.



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Data extraction and management

Two review authors (ZCL, PL) independently extracted data from eligible trials including source of funding, study population, interventions, analyses, and outcomes using standardised data extraction forms. We included data from trials published in duplicate only once. Where necessary, we sought additional information from the principal investigator of the study concerned.

We extracted the following study characteristics.

- Methods: study design, total duration of study, number of study centres and location, study setting.
- Participant characteristics: age, gender, comorbidities, ulcer size and duration, number of ulcers, severity of ulcers as defined by trialists, associated pain, quality of life, inclusion criteria, and exclusion criteria.
- Interventions: intervention, comparison, standard therapies, concomitant therapies, and excluded therapies.
- Outcomes: the measurement scale, direction of the scale, the mean and standard deviation, number of participants per treatment group for continuous outcomes (such as mean pain and quality of life), number of events and number of participants per treatment group for dichotomous outcomes (such as number healed, number with recurrence, adverse events), and hazard ratios and associated 95% confidence intervals for time-to-event outcomes (time to complete healing) as outlined in Types of outcome measures and time points reported.
- Risk of bias of the trial as outlined below in Assessment of risk of bias in included studies.
- Notes: funding for trial, and notable declarations of interest of trial authors.

Some outcome data was not reported in suitable form for meta-analysis. Where possible, missing data were calculated or estimated from a graph or imputed; this was noted in the Characteristics of included studies tables.

Assessment of risk of bias in included studies

Two review authors (ZCL, PL) independently assessed the risk of bias of each included study against key criteria recommended by Cochrane (Higgins 2011a). The domains were as follows:

- random sequence generation
- allocation concealment
- blinding of participants, personnel, and outcome assessors
- incomplete outcome data
- selective outcome reporting
- other sources of bias (e.g. if groups were similar at baseline for important prognostic indicators such as wound size and duration of ulcer; and if co-interventions were monitored or similar between the treatment and control groups).

We explicitly judged each of these criteria as low, high, or unclear risk of bias (either lack of information or uncertainty over the potential for bias) and recorded this information in the 'Risk of bias' table for each included study, see Appendix 2. Any disagreements were resolved by consensus for by consulting a third review author (CW) when necessary. Based on the overall risk of bias of each study and its likely effect on a given outcome, we downgraded the certainty of outcome results for studies where there is a high risk of bias through the GRADE approach.

Measures of treatment effect

The results of each included study were plotted as point estimates, that is risk ratio (RR) with corresponding 95% confidence interval (CI) for dichotomous outcomes (number healed, recurrence); mean difference (MD) and 95% CI for continuous outcomes (e.g. pain, quality of life); and hazard ratio (HR) and 95% CI for time-to-event outcomes (e.g. time to complete healing).

When the results could not be presented in this way, we described the results in the Characteristics of included studies table and reported them within the narrative of text in the review. For dichotomous outcomes with a statistically significant difference between groups, we calculated the number needed to treat for an additional beneficial outcome of healing and number needed to treat for one additional adverse event using the Cates online calculator (Cates 2008).

For continuous measures, we calculated MD for ease of interpretation. We did not have to compare any continuous outcomes across trials and as such did not calculate standardised mean differences (SMD) (Schünemann 2011b).

Unit of analysis issues

None of the included RCTs randomised or allocated clusters (e.g. clinics), hence we did not have to re-analyse such studies by calculating effective sample sizes according to the methods outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b). There was no need to incorporate an estimate of the intracluster coefficient (ICC) using external estimates obtained from similar studies (Higgins 2011b). Consequently, no studies were excluded from the main analysis.

We noted that in studies where people were randomised and received treatment in two legs, a separate outcome was measured from each leg, and the number of legs was used as the denominator in the analysis without adjustment for the non-independence. In such cases there was a potential unit of analysis error. In these studies, we extracted outcomes using the number of people randomised as the denominator (e.g. if we could extract the outcome for just one leg, or if the trialists adjusted their analysis to account for the two legs). Since the studies had been adjusted to account for two legs, there were no exclusions from the primary analyses.

Where multiple trial arms were reported in a single trial, we included only the two relevant arms in a single meta-analysis. For trials presenting outcomes at multiple time points, we extracted data at all time points (0 to 6 months, 6 to 12 months, 12 to 24 months, and latest time point) as subgroups.

Dealing with missing data

We attempted to contact the trial authors to obtain information that was missing from trial reports.

For dichotomous outcomes, we used the number randomised as the denominator, assuming that any participants at the end of treatment did not have a positive outcome (e.g. for the outcome of recurrence, we assumed any missing participants had recurrence;

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for the outcome of healing, we assumed missing participants did not heal).

For continuous outcomes (e.g. mean pain), we calculated the MD or SMD based on the number of participants analysed at that time point. Where the number of participants analysed was not presented for each time point, and the trialists did not report imputed data for missing outcomes, we used the number of randomised participants in each group at baseline.

There were no missing standard deviations that could be computed from other statistics such as standard errors, confidence intervals, or P values, nor did we impute any standard deviations (e.g. from other studies in the meta-analysis). We used this method per the recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011c).

For time-to-event data (e.g. time to complete healing), we extracted HR and 95% CI if this information was reported in the individual trials. If HR and 95% CI were not reported, we obtained estimates of log hazard ratios and their standard errors from other data reported in the trial, as recommended by Parma and Tierney (Parmar 1998; Tierney 2007).

Assessment of heterogeneity

We assessed clinical and methodological diversity in terms of participants, interventions, outcomes, and study characteristics for the included studies to determine whether a meta-analysis was appropriate by observing data from the data extraction tables. We were able to conduct a meta-analysis for one outcome as detailed in later sections.

We assessed statistical heterogeneity between the two studies that examined the same intervention by visual inspection of a forest plot. We used the I^2 statistic to quantify the possible magnitude of and the Chi^2 statistic to assess the statistical significance of heterogeneity.

As recommended in the *Cochrane Handbook* (Deeks 2011), we considered an I^2 value of 0% to 40% might not be important; 30% to 60% may represent moderate heterogeneity; 50% to 90% may represent substantial heterogeneity; and 75% to 100% to represent considerable heterogeneity.

We interpreted the Chi^2 statistic such that a P value ≤ 0.10 indicates evidence of statistical heterogeneity.

In the single meta-analysis conducted, we were unable to investigate the cause of heterogeneity due to the poor design of the RCTs and data provided.

Assessment of reporting biases

We planned to create funnel plots to explore the possible presence of small-study biases, provided we were able to pool data from more than 10 trials for meta-analysis of a primary outcome (Sterne 2011). However, due to the small number of eligible studies this was not possible.

We planned to compare trial protocols against published reports to assess outcome reporting bias. For studies published after 1 July 2005, we screened the WHO ICTRP (apps.who.int/trialsearch/Default.aspx) and the US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov/) for the a priori trial protocol. However, as we identified no protocols for the included trials, we performed no comparison.

Data synthesis

For clinically homogeneous studies with similar participants and comparators and using the same outcome measure, we pooled outcomes in a meta-analysis, using the random-effects model as the default. We planned to use the fixed-effect model in a sensitivity analysis to assess the possibility of small-sample bias, however this was not required.

For time-to-event data (e.g. time to complete healing), we intended to enter log HR and standard error into Review Manager 5 and use generic inverse-variance meta-analysis to pool the HRs (Deeks 2011). However, this was not possible, as there were no two studies with the same intervention and comparator reporting these outcomes.

For dichotomous outcomes, the absolute risk difference was calculated using the risk difference statistic in Review Manager 5 (RevMan 2014), and the result expressed as a percentage. For continuous outcomes, the absolute benefit or change and the relative difference in the change from baseline was calculated, and the absolute benefit divided by the baseline mean of the control group, expressed as a percentage.

'Summary of findings' tables and GRADE assessment of the certainty of evidence

We presented the main results of the review in 'Summary of findings' tables, which communicate information about the three different comparator-intervention designs of included studies. These are: SEPS + compression treatment versus compression treatment alone (Summary of findings for the main comparison); SEPS versus the Linton procedure (Summary of findings 2); and SEPS + saphenous surgery versus saphenous surgery alone (Summary of findings 3).

We recorded key information regarding the certainty of the evidence, magnitude of the effects of the interventions examined, and sum of available data for the main outcomes (Schünemann 2011a). The certainty of the evidence contributing to each outcome was independently assessed by two review authors using the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) (Schünemann 2011a), employing GRADEpro software (GRADEpro 2015). We recorded the rationale behind all decisions to downgrade the certainty of the evidence in footnotes.

In cases where studies had a high risk of reporting bias, we downgraded the certainty of the evidence once. We further downgraded the certainty of the evidence once if two or more other 'Risk of bias' domains were assessed as unclear or high risk; this included the instance when there was unclear risk of reporting bias.

We also downgraded the certainty of the evidence once for imprecision and twice for serious imprecision owing to small and very small sample sizes, respectively.

We present the following outcomes in the 'Summary of findings' tables, at time point 12 to 24 months:

- number of people with ulcers healed;

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- time to complete healing;
- recurrence of ulcers;
- quality of life;
- number of adverse events;
- pain.

Subgroup analysis and investigation of heterogeneity

There were insufficient data (e.g. stratified data presented in the trials) to perform subgroup analyses to determine whether ulcer healing and recurrence are influenced by the following factors:

- participants with type 1 and 2 diabetes mellitus as a comorbidity (versus no diabetes);
- severity of ulcers at baseline determined by size (> 5 cm^2 or ≤ 5 cm^2) and/or ulcer duration (> 6 months or ≤ 6 months).

We therefore did not use the formal test for subgroup interactions in Review Manager 5 (RevMan 2014). The magnitude of the effects if present would have been compared between the subgroups by means of assessing the overlap of the confidence intervals of the summary estimate. Non-overlap of the confidence intervals may indicate statistically significant differences between subgroups.

Sensitivity analysis

There were insufficient data to perform sensitivity analysis. We had planned to assess the robustness of effect estimates for ulcer healing and ulcer recurrence to selection bias (excluding trials with inadequate or unclear allocation concealment); detection bias (excluding trials with unclear or inadequate blinding of outcome assessors); and attrition bias (excluding trials with incomplete outcome data). However, as all trials were subject to these biases, we could not limit analyses to studies at low risk of bias.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies

Results of the search

The search of the Cochrane Wounds Specialised Register, CENTRAL, MEDLINE, Embase, and CINAHL yielded 162 titles and abstracts. A handsearch identified no other records. We therefore screened 162 citations, excluding two because they were duplicates and 148 that were not RCTs, did not involve SEPS, or investigated other populations (e.g. people with varicose veins and without venous leg ulcers). After screening the citations, we identified 12 records for full-text evaluation. We excluded eight studies after full-text evaluation as they did not meet the inclusion criteria (Figure 1).

Four studies (six records) met our inclusion criteria (Callini 2002; Nelzen 2011; Pierik 1997; Van Gent 2006). Two records were additional publications from the same study; as such, data from Wittens 2004 were extracted with Van Gent 2006, and Sybrandy 2001 with Pierik 1997. We attempted to contact the authors of Callini 2002 and Nelzen 2011 for further clarification of trial methods and results, however none of the authors replied with this information.

Included studies

Four RCTs with a total of 322 participants met the inclusion criteria. The most recent trial was published in 2011 (Nelzen 2011), and the earliest trial was published in 1997 (Pierik 1997).

Both Callini 2002 and Van Gent 2006 compared SEPS plus compression therapy with compression therapy only. Callini 2002 provided no further details about the intervention. In Van Gent 2006, participants who underwent SEPS also received concomitant treatment of superficial venous incompetence where indicated.

Van Gent 2006 was conducted at multiple centres in the Netherlands, and involved 200 participants followed for up to 29 months. They recruited participants with first-time ulcer or recurrent ulceration and compared SEPS and compression therapy with compression therapy alone. They reported the outcomes of venous leg ulcer healing and recurrence rates, but did not report adverse events.

Callini 2002 was a small RCT arm containing 12 participants within a larger study. Translated from Italian to English, the paper reported results of participants with venous insufficiency, some of whom had venous leg ulcers. Minimal information was available regarding participants and methods.

Pierik 1997 was conducted at multiple centres in the Netherlands, and enrolled 39 participants followed for up to 60 months. The study compared SEPS with the Linton procedure, an open surgical method with an otherwise similar approach to ligating perforator veins. All included participants had failed one or more conservative treatments. Both groups were treated with compression therapy postsurgery to promote wound and ulcer healing. The trialists ended the trial early, at the 15-month mark, due to significantly higher adverse events noted in the Linton group.

Nelzen 2011 enrolled 75 participants across multiple community hospitals in Sweden who were followed for up to 12 months. The study compared SEPS with saphenous surgery to saphenous surgery alone. Participants were stratified according to Clinical-Etiology-Anatomy-Pathophysiology (CEAP) classification C6 and C5. Saphenous surgery involved removal or obliteration of the great and small saphenous veins close to the sapheno-popliteal junction. Some participants in both groups used compression postoperatively, however their relative distribution and adherence were not reported. We attempted to contact the authors for clarification, but did not receive a reply.

All of the included studies with the exception of Callini 2002 reported trial methodology and ethics approval from university ethics committees.

No sources of funding were reported for Pierik 1997 and Callini 2002. Nelzen 2011 was funded by the Skaraborg Hospital Research & Development Fund, and Van Gent 2006 was funded by the Dutch government.

Not all included studies reported key baseline characteristics such as ulcer size and duration; only two studies reported duration (Nelzen 2011; Pierik 1997), and two reported size (Pierik 1997; Van Gent 2006). No baseline characteristics were reported by Callini 2002. Full details of the included studies are summarised in the Characteristics of included studies table.

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None of the trials reported serious adverse events, quality of life, pain, or district nursing care requirements.

Excluded studies

At the full text screening stage we excluded eight studies for the following reasons: three were not RCTs (Gloviczki 1999; Gloviczki 2000; Jeanneret 2003); one did not include participants with venous leg ulcers (Sharma 2011); two did not involve SEPS (Taradaj 2011; Warburg 1994); and we could not isolate the effect of SEPS alone in two studies: Gan 2013 included an intervention additional to SEPS in comparison with conservative management, and Wang 2009 compared two different areas of SEPS application (see Characteristics of excluded studies table).

Risk of bias in included studies

A summary of the 'Risk of bias' assessment according to the criteria described in the *Cochrane Handbook for Systematic Reviews of Interventions* is outlined in Figure 2 and Figure 3 (Higgins 2011a).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

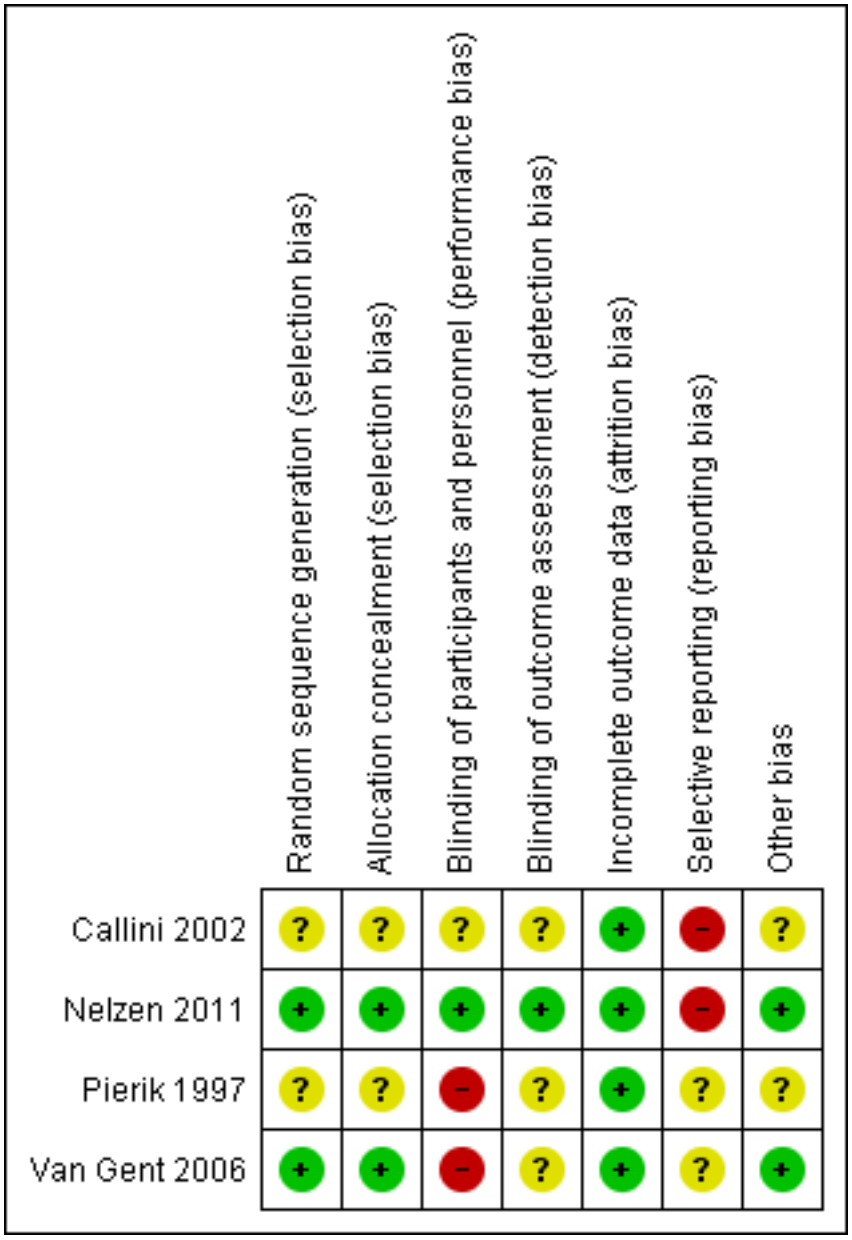

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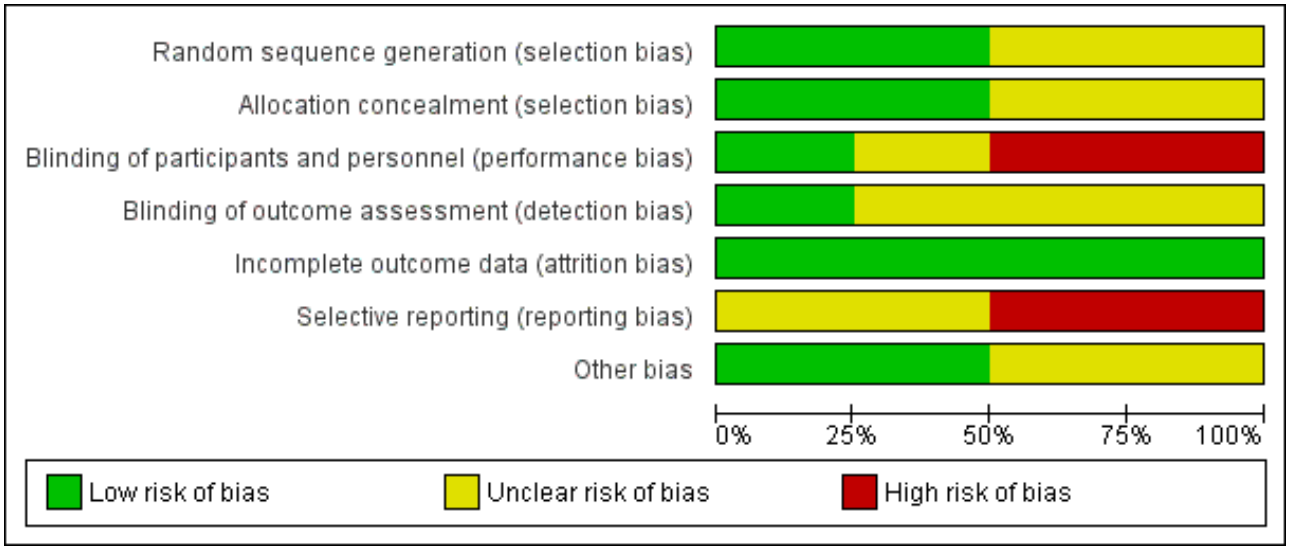
Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

Two studies reported the randomisation process in sufficient detail to indicate that adequate methods were used and were assessed as at low risk of selection bias: one study utilised an independent randomisation centre (Van Gent 2006), whilst the other assigned participants to separate groups in the operating theatre through the opening of sealed envelopes (Nelzen 2011). We judged two studies as at unclear risk of selection bias, as they did not report randomisation and allocation methods in sufficient detail to make a judgement of high or low risk (Callini 2002; Pierik 1997).

Blinding

Due to the nature of the surgical interventions, there was no possibility of blinding the surgeon to the procedure involved. However, participants in both treatment groups in Nelzen 2011 had surgery, and surgical incisions were concealed, thus we judged there was an overall low risk of performance bias in this study.

All studies reported blinding of the participants before the commencement of the intervention, however it is highly unlikely that participants in most of the included studies could have remained blinded. The control group in Van Gent 2006 did not undergo surgery of any kind, therefore their allocation would have been obvious. The surgical incisions in Pierik 1997 would have indicated the intervention to the participant and assessors postsurgery. Callini 2002 had no trial methodology and was therefore assessed as at unclear risk of performance bias.

The definition of complete healing (100% epithelialisation, no exudate or scab) is subjective, and assessment may vary between clinicians. Nelzen 2011 reported that the wound-healing assessor was blinded, and we therefore assessed this study to have a low risk of detection bias. There was an unclear risk of detection bias for Callini 2002, Pierik 1997 and Van Gent 2006, as the authors did not report if the assessor was blinded.

Incomplete outcome data

There was a low risk of attrition bias in the three largest included studies. After randomisation in the Van Gent 2006 trial, only (4/200: 2%) of participants were omitted from the analysis: 3 did not undergo the SEPS procedure, and 1 was lost to follow-up. Follow-up was complete in all but (2/39: 5%) participants in Pierik 1997, one from each group.

Nelzen 2011 did not account for the (1/75: 1%) participant that was lost to follow-up and missing from the outcome assessment, but we judged the overall associated risk with such a small omission to be small.

Selective reporting

We rated two studies as at unclear risk of reporting bias due to the lack of protocols prior to the commencement of the RCT (Pierik 1997; Van Gent 2006). Van Gent 2006 furthermore did not report adverse events as an outcome.

The trials reported by Nelzen 2011 and Callini 2002 did not publish protocols, and were rated as at high risk of bias due to unclear reporting of outcome data. In both papers postoperative symptoms or recurrence were not clearly attributed to either treatment group.

Other potential sources of bias

In Callini 2002, it was unclear if any co-interventions were applied equally between the treatment and control groups, which was considered a potential additional source of bias. There were no clearly identified other potential sources of bias in Nelzen 2011, Pierik 1997, or Van Gent 2006.

Effects of interventions

See: **Summary of findings for the main comparison** Subfascial endoscopic perforator vein surgery (SEPS) + compression versus compression alone for treating venous leg ulcers; **Summary of findings 2** Subfascial endoscopic perforator vein surgery (SEPS) compared to the Linton procedure for treating venous leg ulcers; **Summary of findings 3** Subfascial endoscopic perforator vein

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surgery (SEPS) + saphenous surgery compared to saphenous surgery for treating venous leg ulcers

Due to the largely different comparisons of the trials, we were only able to perform one meta-analysis, combining two trials for the outcome of ulcer recurrence at 12 to 24 months in the SEPS plus compression therapy versus compression therapy alone comparison (Callini 2002; Van Gent 2006). As the other trials reported differing comparisons, we have reported these results separately.

Comparison 1: SEPS + compression therapy versus compression therapy (2 studies; 208 participants)

See: Summary of findings for the main comparison

Two studies compared the addition of SEPS with compression therapy for venous leg ulcers (Callini 2002; Van Gent 2006). For ease of description, the group that received SEPS and compression therapy is referred to as the 'SEPS' group and the group with just compression therapy as the 'no SEPS' group.

Primary outcome 1: venous leg ulcer healing (proportion healed within time points)

Van Gent 2006 reported the proportion of ulcers healed at multiple time points (6, 12, and 24 months).

At 6 months, it is uncertain whether SEPS was associated with a larger proportion of healed ulcers (risk ratio (RR) 1.11, 95% confidence interval (CI) 0.86 to 1.42; Analysis 1.1)

At 12 months, it is uncertain whether SEPS was associated with a larger proportion of healed ulcers (RR 1.15, 95% CI 0.96 to 1.39; Analysis 1.1).

At 24 months (latest timepoint) SEPS may result in a larger proportion of participants with healed ulcers (RR 1.17, 95% CI 1.03 to 1.33; Analysis 1.1). We consider the evidence to be of low certainty, downgraded once for imprecision and once for risk of bias.

Primary outcome 2: recurrence of venous leg ulcer (proportion recurrence within time points)

At 6 months, it is uncertain whether SEPS reduces the risk of ulcer recurrence (RR 0.62, 95% CI 0.27 to 1.41; Analysis 1.2).

At 12 months, it is uncertain whether SEPS reduces the risk of ulcer recurrence (RR 0.72, 95% CI 0.37 to 1.42; Analysis 1.2).

We were able to pool the data from Callini 2002 and Van Gent 2006 (208 participants) into a meta-analysis for this outcome at 24 months, analysing the data using a random-effects model.

At 24 months (latest timepoint), it is uncertain whether SEPS reduces the risk of ulcer recurrence (RR 0.85, 95% CI 0.26 to 2.76; Analysis 1.2). We consider the evidence to be of very low certainty, downgraded once for risk of bias and twice for very serious imprecision due to small sample size and wide confidence intervals.

Other outcomes

Neither study measured or reported time to complete healing, health-related quality of life, pain, duration of hospitalisation, or district nursing care requirements. It is unclear if adverse events or serious adverse events occurred in either study, as these were not measured or reported.

Comparison 2: SEPS versus Linton procedure (1 study; 39 participants)

See: Summary of findings 2

One study compared the use of SEPS with the Linton procedure for the treatment of venous leg ulcers (Pierik 1997).

Primary outcome 1: venous leg ulcer healing (proportion healed within time points)

At 6 months, it is uncertain whether SEPS is associated with a decreased proportion of healed ulcers (RR 0.95, 95% CI 0.75 to 1.21; Analysis 2.1).

At 12 months, it is uncertain whether SEPS is associated with a decreased proportion of healed ulcers (RR 0.90, 95% CI 0.73 to 1.11; Analysis 2.1).

At 24 months (latest timepoint), it is also uncertain whether SEPS is associated with a decreased proportion of healed ulcers (RR 0.95, 95% CI 0.83 to 1.09; Analysis 2.1). We consider the evidence to be of very low certainty, downgraded once for risk of bias and twice for very serious imprecision due to very small sample sizes.

Primary outcome 2: recurrence of venous leg ulcer (proportion recurrence within time points)

The only analysed time point for the recurrence of venous leg ulcers in Pierik 1997 was at 60 months.

At 60 months (latest timepoint) it is uncertain whether SEPS reduces the risk of ulcer recurrence (RR 0.47, 95% CI 0.10 to 2.30; Analysis 2.2). We consider the evidence to be of very low certainty, downgraded once for risk of bias and twice for very serious imprecision due to very small sample sizes.

Secondary outcome 1: adverse events

Recruitment for the trial reported by Pierik 1997 was stopped early due to a significant difference between the Linton group and the SEPS group in adverse events. It is uncertain whether SEPS reduces the risk of adverse events at 15 months post-procedure (latest timepoint): (RR 0.04, 95% CI 0.00 to 0.60; Analysis 2.3). We consider the evidence to be of very low certainty, downgraded once for risk of bias and twice for very serious imprecision due to very small sample sizes.

These adverse events included superficial and deep wound infections (10 cases) as well as nerve damage (2 cases) found immediately postoperatively.

Secondary outcome 2: serious adverse events

Pierik 1997 did not delineate 'serious adverse events' as an outcome in their study, however the authors reported one death due to myocardial infarction in the SEPS group five months after the procedure, and two participants in the Linton group were readmitted due to serious wound complications. Regarding the former, the myocardial infarction was unlikely to have been related to the procedure, therefore we have not considered it to be an 'event' for this outcome. As such, it is unclear whether SEPS was

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associated with fewer serious adverse events (RR 0.19, 95% CI 0.01 to 3.73). We consider the evidence to be of very low certainty, downgraded once for risk of bias and twice for very serious imprecision due to very small sample sizes.

Other outcomes

The mean duration of hospitalisation recorded in Pierik 1997 was higher in participants in the Linton group (7 days, range 3 to 39) compared with those in the SEPS group (4 days, range 2 to 6) (P < 0.001). We were unable to independently calculate the mean difference due to lack of further statistical information, and our attempts to obtain additional information were unsuccessful.

There were no measured or reported outcomes of time to complete healing, health-related quality of life, pain, or district nursing care requirements.

Comparison 3: SEPS + saphenous surgery versus saphenous surgery (1 study; 75 participants)

See: Summary of findings 3

One study compared the use of SEPS in addition to saphenous surgery ('SEPS group') with saphenous alone ('no SEPS group') to investigate the efficacy of SEPS as an adjunct for venous leg ulcer treatment (Nelzen 2011).

Primary outcome 1: venous leg ulcer healing (proportion healed within time points)

In this study the groups were stratified at randomisation according to the presence of active ulcers (CEAP classification C6) or healed ulcers (CEAP classification C5). Based on our inclusion criteria (active ulcers), we have only included the C6 subgroup in our analysis.

At 12 months (latest time point), it is uncertain whether SEPS is associated with a decreased proportion of healed ulcers (RR 0.96, 95% CI 0.64 to 1.43; Analysis 3.1). We consider the evidence to be of very low certainty, downgraded once for risk of bias and twice for very serious imprecision due to very small sample sizes.

Primary outcome 2: recurrence of venous leg ulcer (proportion recurrence within time points)

At 6 months, it is uncertain whether SEPS increased the recurrence of ulceration (RR 1.03, 95% CI 0.28 to 3.81; Analysis 3.2).

At 12 months (latest timepoint), it is uncertain whether SEPS increased the recurrence of ulceration (RR 1.03, 95% CI 0.15 to 6.91; Analysis 3.2). We consider the evidence to be of very low certainty, downgraded once for risk of bias and twice for very serious imprecision due to very small sample sizes and wide confidence interval.

Secondary outcome 1: adverse events

Nelzen 2011 reported adverse events up to 30 days (latest time point) after the operation.

It is uncertain whether SEPS was associated with more adverse events (RR 2.05, 95% CI 0.86 to 4.90; Analysis 3.3). We consider the evidence to be of very low certainty, downgraded once for risk of bias and twice for very serious imprecision due to very small sample sizes and wide confidence interval.

Other outcomes

There were no measured or reported outcomes of health-related quality of life, serious adverse events, duration of hospitalisation, or district nursing care requirements.

Pain was reported as an adverse event but only as a dichotomous outcome. The trial also described participants' symptoms before and after surgery at 3 and 12 months, in which participants self reported as having 'severe', 'some', 'minor', or 'no' symptoms. However, data from both groups were pooled into a single figure, and the definition of 'symptoms' was not provided. There was no quantification of pain scales.

Nelzen 2011 also reported mean time to healing as one of the outcomes of the study. However, it was unclear whether all participants experienced wound healing as part of the analysis. The data presented were insufficient, as such, we were unable to calculate a mean difference for this outcome.

We were unable to obtain the above information from the study authors, and were therefore unable to extract any data relevant to our review outcomes.

DISCUSSION

Summary of main results

The aim of this review was to summarise and interpret the evidence of SEPS to assess the efficacy, benefits, and harms in the treatment of venous leg ulcers. We identified four RCTs, reported by six papers, with 322 randomised participants. The results have been split according to interventions for ease of interpretation.

SEPS + compression therapy versus compression therapy

SEPS may improve venous leg ulcer healing rates at 24 months based on the results of one trial (low-certainty evidence). Regarding ulcer recurrence, we assessed the evidence from two studies as of very low certainty, therefore it is unclear if SEPS is beneficial compared with compression therapy. Our GRADE assessment of the evidence as low or very low certainty was due to risk of bias, small sample sizes, and wide confidence intervals.

Time to complete healing, health-related quality of life, pain, duration of hospitalisation, and district nursing care requirements were not measured or reported. Furthermore, it is unclear if adverse events or serious adverse events occurred in either study, as these were not reported or measured.

SEPS versus the Linton procedure

We identified only very low-certainty evidence from a single small trial for this comparison, thus we are uncertain if there is a difference between SEPS and the Linton procedure in terms of ulcer healing and recurrence. The Linton procedure may be associated with prolonged hospitalisation and a higher number of adverse events compared with SEPS, but this was ultimately unclear due to the very low certainty of the evidence. Our GRADE assessment of the evidence as very low certainty was due to risk of bias, small sample sizes, and wide confidence intervals.

Time to complete healing, health-related quality of life, pain and district nursing care requirements were not measured or reported.

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SEPS + saphenous surgery versus saphenous surgery

We are uncertain if SEPS added to saphenous surgery alters ulcer healing or ulcer recurrence due to very low-certainty evidence from a single trial. It is also uncertain if there is a difference in adverse events between groups due to small event rates (very low-certainty evidence). Our GRADE assessment of the evidence as very low certainty was due to high risk of reporting bias, small sample sizes, and wide confidence intervals.

Time to complete healing data were not available for analysis. Health-related quality of life, serious adverse events, duration of hospitalisation, and district nursing care requirements were not measured or reported.

Overall completeness and applicability of evidence

The included studies have clinical applicability in their outcomes, as they were all performed in a hospital setting as part of clinical management. Only two studies evaluated the same comparison and therefore permitted meta-analysis, whilst the other two studies examined different comparators with SEPS.

Due to lack of studies and data in the included trials, we were unable to conduct the prespecified subgroup analyses.

Given the clearly established participant groups in all the studies, the evidence can be applied to any participant who suffers from venous leg ulcers. There were clear inclusion and exclusion criteria in the studies, with the exception of Callini 2002. The outcomes examined were also clinically applicable and play an important role in the decision-making process regarding treatment of these patients. However, the evidence is limited by the statistical power of the studies (small sample size).

We cannot be certain of the risk ratio of SEPS due to the lack of reporting of important outcomes such as quality of life, time to complete healing, and adverse events.

Pierik 1997 reported a clear increase in the rate of postoperative adverse events with the Linton approach compared with SEPS. This was applied as a discussion point in all the later trials examined in this review, and has influenced the cessation of the Linton approach in many clinical centres.

The completeness of the evidence was limited by the failure of trials to report important outcomes. Time to complete healing was not reported or was reported with limited data in three trials; adverse events were omitted from two trials; and the small number of events and participants means we are uncertain of the risks of adverse events. Quality of life, district nursing care requirements and pain were also not reported in any of the trials, and only one study evaluated an outcome related to costs (duration of hospitalisation).

Quality of the evidence

Only low- or very low-certainty evidence was available for each outcome included in this review, and most of the evidence was downgraded due to imprecision and risk of reporting, selection, performance, and/or detection biases (Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3). There was no indirectness, as the evidence was within the scope of the review. We did not downgrade for publication bias or inconsistency as most of the studies were not pooled. Further studies are likely to change the results of our conclusions by strengthening the evidence. We suspect that the lack of studies relevant to our review suggests a lack of research into SEPS rather than publication bias.

SEPS + compression therapy versus compression therapy

We found only low- and very low-certainty evidence for this comparison for the outcomes of ulcer healing and ulcer recurrence. We downgraded the evidence due to imprecision owing to the small sample size and wide confidence intervals, unclear risk of detection and reporting bias due to lack of protocols and the potential for unreported outcomes (e.g. adverse events), and high risk of performance bias.

We were only able to complete one meta-analysis, for the outcome of ulcer recurrence at 24 months. The study sample sizes were below 200 for all included trials, which limited the precision of the evidence.

For the meta-analysis, one study had an overall unclear risk of selection, performance, detection, and other biases due to the lack of information about methodology and no reporting of participant baseline characteristics or adverse events (Callini 2002). Van Gent 2006 was assessed as at low risk of bias overall, however blinding of participants was difficult (unclear risk of detection bias), and the authors did not publish a protocol prior to the RCT implementation or report adverse events (unclear risk of reporting bias). The sample size of the meta-analysis was small and the confidence interval range large, leading to further downgrading of the evidence. As such, the certainty of the evidence for this outcome is very low, and we were unable to ascertain the effect of SEPS on venous leg ulcer recurrence (Summary of findings for the main comparison).

There were no available data for analysis for the outcomes of time to complete healing, health-related quality of life, adverse events, pain, duration of hospitalisation, and district nursing care requirements.

SEPS versus the Linton procedure

We found only very low-certainty evidence from one study for the outcomes of ulcer healing, ulcer recurrence (60 months), and adverse events. We downgraded the evidence twice due to imprecision owing to the very small sample size, and once for unclear risk of selection, detection, reporting, and other biases and high risk of performance bias due to the trial design and lack of a protocol.

There were no available data for analysis for the outcome of duration of hospitalisation and no measured or reported outcomes of time to complete healing, health-related quality of life, pain and district nursing care requirements.

SEPS + saphenous surgery versus saphenous surgery

We found only very low-certainty evidence from a single study for the outcomes of ulcer healing, ulcer recurrence, and adverse events. We downgraded the evidence twice due to imprecision owing to the small sample size or wide confidence intervals, and once for high risk of reporting bias due to the trial design and lack of a protocol.

There were no available data for analysis for the outcome of time to complete healing and no measured or reported outcomes of

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health-related quality of life, serious adverse events, duration of hospitalisation, and district nursing care requirements.

Potential biases in the review process

There was potential bias in the review process as detailed below, however strict adherence to Cochrane methods helped to avoid bias where possible.

We are confident that we used a broad literature search and captured all relevant literature for this topic. Two review authors independently assessed the trials, extracted data, assessed risk of bias, and graded the evidence in order to minimise bias. In the event that the two review authors were not able to reach consensus, a third review author made the final decision.

However, despite an extensive search, it is possible that some trials may have be missed. We invite readers to notify us of any RCTs, published or unpublished, that meet the selection criteria.

We also note that the influence of funders can add an other potential source of bias. Funders may not publish results of negative trials, leading to publication bias, or funder-sponsored trials may include an inappropriate comparator, for example suboptimal dose or non-standard practice, so that their intervention looks better, potentially affecting the applicability and generalisability of results.

With regard to bias arising from differences between protocol and review stages, we have highlighted this information in the Differences between protocol and review section. Due to an error identified post publication, we noted that we would include studies that involved SEPS and other concurrent interventions if we were able to isolate the effects of SEPS (e.g. if SEPS was the only dependent variable, i.e. SEPS + saphenous surgery versus saphenous surgery).

Finally, interpreting ulcer recurrence data from trials where not all participants had healed ulcers at the end of follow up may not accurately reflect the outcome in the randomised population. A similar instance is also demonstrated in Nelzen 2011 where a subgroup of trial data was used in the calculation of proportion of ulcers healed (primary outcome 1).

Agreements and disagreements with other studies or reviews

Luebke 2009 was a meta-analysis that examined SEPS in comparison to other techniques for the management of chronic venous insufficiency. As venous leg ulcers are a complication of chronic venous insufficiency, some of the analyses in the paper could be considered for comparison with our review. We included the study reported by Pierik 1997 similar to Luebke 2009, however the other studies did not fit our inclusion criteria requiring participants with venous leg ulcers and not venous insufficiency alone.

In a similar Cochrane Review investigating surgery for deep venous incompetence (Goel 2015), the authors excluded SEPS as a comparator, thus Goel 2015 was not applicable for comparison with this review.

AUTHORS' CONCLUSIONS

Implications for practice

SEPS in combination with compression therapy may improve healing of venous leg ulcers compared with compression therapy alone (low-certainty evidence). From the data included in this review, we are uncertain if it reduces the recurrence of venous leg ulcers (very-low certainty evidence). However, as we did not consider trials that recruited people with closed venous leg ulcers, this limits the conclusions we can make about recurrence. Due to the low or very low certainty of the currently available evidence, we are unable to draw conclusions as to the effect of SEPS when used in combination with other surgical techniques. We are also unable to draw conclusions regarding the safety of SEPS compared with other interventions from included trial data due to the small number of reported adverse events and biases in study designs (very low-certainty evidence).

Implications for research

There are only a few small randomised controlled trials on this topic. A number of clinically important outcomes included in our protocol such as time to complete healing, quality of life, pain, and district nursing care requirements could not be fully assessed due to lack of studies and reporting of adverse events.

Further research that includes measurement and reporting of these outcomes would thus give a more holistic view of SEPS as a treatment option and establish more rigorous evidence as to whether SEPS is a clinically effective treatment in people with venous leg ulcers. In addition, trials with larger numbers of participants and strict inclusion criteria for active ulceration are likely to give greater certainty to the evidence and outcomes presented.

Notably the Australian and European clinical practice guidelines acknowledge that SEPS is an ongoing area of research (Franks 2016), and additional randomised controlled trials on this topic are warranted. However, no studies or protocols have been published since 2011. Depending on further research into the area, this review may need to be updated.

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REFERENCES

References to studies included in this review

Callini 2002 *{published data only}*

Callini E, D'Angelo F, Colombo R, Vaghi M, Zorzoli C. Venous stasis ulcers: endoscopic treatment. *Impegno Ospedaliero Sezione Scientifica* 2002;**23**(1-2):9-13.

Nelzen 2011 *{published data only}*

Nelzen O, Fransson I. Early results from a randomized trial of saphenous surgery with or without subfascial endoscopic perforator surgery in patients with a venous ulcer. *British Journal of Surgery* 2011;**98**(4):495-500.

Pierik 1997 *{published data only}*

* Pierik EG, Van Urk H, Hop WC, Wittens CH. Endoscopic versus open subfascial division of incompetent perforating veins in the treatment of venous leg ulceration: a randomized trial. *Journal of Vascular Surgery* 1997;**26**(6):1049-54.

Sybrandy JE, Van Gent WB, Pierik EG, Wittens CH. Endoscopic versus open subfascial division of incompetent perforating veins in the treatment of venous leg ulceration: long-term follow-up. *Journal of Vascular Surgery* 2001;**33**(5):1028-32.

Van Gent 2006 *{published data only}*

* Van Gent WB, Hop WC, van Praag MC, Mackaay AJ, De Boer EM, Wittens CH. Conservative versus surgical treatment of venous leg ulcers: a prospective, randomized, multicenter trial. *Journal of Vascular Surgery* 2006;**44**(3):563-71.

Wittens CH, Van Gent WB, Hop WC. Conservative versus surgical treatment of venous leg ulcers (Dutch SEPS trial). *Phlebology/ Venous Forum of the Royal Society of Medicine* 2004;**19**(3):157.

References to studies excluded from this review

Gan 2013 *{published data only}*

Gan SJ, Qian SX, Zhang C, Mao JQ, Li K, Tang JQ. Combined subfascial endoscopic perforator surgery and endovenous laser treatment without impact on the great saphenous vein for management of lower-extremity varicose veins. *Chinese Medical Journal* 2013;**126**(3):405-8.

Gloviczki 1999 *{published data only}*

Gloviczki P. Subfascial endoscopic perforator vein surgery: indications and results. *Vascular Medicine* 1999;**4**:178-80.

Gloviczki 2000 *{published data only}*

Gloviczki P. Surgical treatment of the superficial and perforating veins. *Phlebology/Venous Forum of the Royal Society of Medicine* 2000;**15**(3-4):131-6.

Jeanneret 2003 *{published data only}*

Jeanneret C, Fischer R, Chandler JG, Galeazzi RL, Jager KA. Great saphenous vein stripping with liberal use of subfascial endoscopic perforator vein surgery (SEPS). *Annals of Vascular Surgery* 2003;**17**(5):539-49.

Sharma 2011 *{published data only}*

Sharma P. Comparative study of ultrasound-guided foam sclerotherapy and subfascial endoscopic perforator surgery. *Cardiovascular and Interventional Radiology* 2011;**34**:649.

Taradaj 2011 *{published data only}*

Taradaj J, Franek A, Cierpka L, Brzezinska-Wcislo L, Blaszczak E, Polak A, et al. Early and long-term results of physical methods in the treatment of venous leg ulcers: randomized controlled trial. *Phlebology/Venous Forum of the Royal Society of Medicine* 2011;**26**(6):237-45.

Wang 2009 *{published data only}*

Wang MH, Jin X, Zhang SY, Wu XJ, Zhong ZY, Wang M, et al. Lateral subfascial endoscopic perforating vein surgery as treatment for lateral perforating vein incompetence and venous ulceration. *World Journal of Surgery* 2009;**33**(5):1093-8.

Warburg 1994 *{published data only}*

Warburg FE, Danielsen L, Madsen SM, Raaschou HO, Munkvad S, Jensen R, et al. Vein surgery with or without skin grafting versus conservative treatment for leg ulcers. A randomized prospective study. *Acta Dermato-Venereologica* 1994;**74**(4):307-9.

Additional references

Abbade 2005

Abbade LP, Fernandes LS. Venous ulcer: epidemiology, physiopathology, diagnosis and treatment. *International Journal of Dermatology* 2005;**44**(6):449-56.

Alguire 1997

Alguire PC, Mathes BM. Chronic venous insufficiency and venous ulceration. *Journal of General Internal Medicine* 1997;**12**(6):374-83.

Angel 2005

Angel D, Sieunarine K, Abbas M, Mwipatayi B. The difficult leg ulcer: a case review illustrating the problems and difficulties associated with treatment. *Primary Intention* 2005;**13**(1):7-14.

AWMA 2011

Australian Wound Management Association (AWMA). Australian and New Zealand clinical practice guideline for prevention and management of venous leg ulcers. www.nzwcs.org.nz/images/luag/2011_awma_vlug.pdf (accessed 12 December 2018).

Bacon 2009

Bacon JL, Dinneen AJ, Marsh P, Holdstock JM, Price BA, Whiteley MS. Five-year results of incompetent perforator vein closure using TRans-Luminal Occlusion of Perforator. *Phlebology* 2009;**24**(2):74-8.

Baker 1991

Baker SR, Stacey MC, Jopp-McKay AG, Hoskin SE, Thompson PJ. Epidemiology of chronic venous ulcers. *British Journal of Surgery* 1991;**78**(7):864-7.

Copyright © 2019 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Baker 1992

Baker SR, Stacey MC, Singh G, Hoskin SE, Thompson PJ. Aetiology of chronic leg ulcers. *European Journal of Vascular Surgery* 1992;**6**(3):245-61.

Baker 1994

Baker S, Stacey M. Epidemiology of chronic leg ulcers in Australia. *Australia and New Zealand Journal of Surgery* 1994;**64**(4):258-61.

Beebe-Dimmer 2005

Beebe-Dimmer JL, Pfeifer JR, Engle JS, Schottenfeld D. The epidemiology of chronic venous insufficiency and varicose veins. *Annals of Epidemiology* 2005;**15**:175-84.

Bergan 2002

Bergan JJ. Advances in venous surgery: SEPS and phlebectomy for chronic venous insufficiency. *Dermatology Surgery* 2002;**28**(1):26-8.

Burnand 2001

Burnand KG. The physiology and hemodynamics of chronic venous insufficiency of the lower limb. In: Gloviczki P, Yao JS editor(s). Handbook of Venous Disorders. 2nd Edition. London, UK: Arnold, 2001:49-57.

Cates 2008 [Computer program]

Cates C. Visual Rx online NNT Calculator. Version 3.0 (accessed 12 December 2018).

Chen 2007

Chen WY, Rogers AA. Recent insights into the causes of chronic leg ulceration in venous diseases and implications on other types of chronic wounds. *Wound Repair and Regeneration* 2007;**15**:434-49.

De Araujo 2003

De Araujo T, Valencia I, Federman D, Kirsner RS. Managing the patient with venous ulcers. *Annals of Internal Medicine* 2003;**138**(4):326-34.

De Souza 2013

De Souza EM, Yoshida WB, de Melo VA, Arago JA, de Oliveira LA. Ulcer due to chronic venous disease: a sociodemographic study in Northeastern Brazil. *Annals of Vascular Surgery* 2013;**27**(5):571-6.

Deeks 2011

Deeks JJ, Higgins JP, Altman DG, editor(s). Chapter 9: Analysing data and undertaking meta-analyses. In: Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Donnelly 2009

Donnelly R, London NJ, editor(s). ABC of Arterial and Venous Disease. 2nd Edition. Chichester, UK: Wiley-Blackwell/BMJ Books, 2009.

Franks 2016

Franks P, Barker J, Collier M, Gethin G, Haesler E, Jawien A, et al. Management of patients with venous leg ulcers: challenges and current best practice. *Journal of Wound Care* 2016;**25**(6 Suppl):1-67.

Goel 2015

Goel RR, Abidia A, Hardy SC. Surgery for deep venous incompetence. *Cochrane Database of Systematic Reviews* 2015, Issue 2. [DOI: 10.1002/14651858.CD001097.pub3]

Gohel 2018

Gohel MS, Heatley F, Liu X, Bradbury A, Bulbulia R, Cullum N, Epstein D, Nyamekye I, Poskitt K, Renton, S, Warwick J, Davies AH. A Randomized Trial of Early Endovenous Ablation in Venous Ulceration. *The New England Journal of Medicine* 2018;**378**:2105-14.

GRADEpro 2015 [Computer program]

McMaster University (developed by Evidence Prime). GRADEpro Guideline development tool. Version accessed 1 December 2018. Hamilton (ON): McMaster University (developed by Evidence Prime), 2015.

Grey 2006

Grey JE, Harding KG, Enoch S. Venous and arterial leg ulcers. *BMJ* 2006;**332**(7537):347-50.

Hafner 1999

Hafner J, Ramelet A-A, Schmeller W, Brunner UV. Management of leg ulcers. *Current Problems in Dermatology* 1999;**27**:190-4.

Hareendran 2005

Hareendran A, Bradbury A, Budd J, Geroulakos G, Hobbs R, Kenkre J, et al. Measuring the impact of venous leg ulcers on quality of life. *Journal of Wound Care* 2005;**14**(2):53-7.

Hess 2011

Hess T, Cathy BS. Checklist for factors affecting wound healing. *Advances in Skin and Wound Care* 2011;**24**(4):192.

Higgins 2011a

Higgins JP, Altman DG, Sterne JA, editor(s). Chapter 8: Assessing risk of bias in included studies. In: Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Higgins 2011b

Higgins JP, Deeks JJ, Altman DG, editor(s). Chapter 16: Special topics in statistics. In: Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Higgins 2011c

Higgins JP, Deeks JJ, editor(s). Chapter 7: Selecting studies and collecting data. In: Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Copyright © 2019 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Iglesias 2004

Iglesias C, Nelson EA, Cullum NA, Torgerson DJ. VenUS I: a randomised controlled trial of two types of bandage for treating venous leg ulcers. *Health Technology Assessment* 2004;**8**(29):1-105.

Khan 2012

Khan SU, Safiuddin M, Rahman, M. Chronic venous disease: management update. *University Heart Journal* 2012;**8**(1):36-9.

Lang 2001

Lang W. Development of perforator vein surgery from the Linton and Cockett procedure to endoscopic dissection. *Zentralblatt für Chirurgie* 2001;**126**(7):495-500.

Luebke 2009

Luebke T, Brunkwall J. Meta-analysis of subfascial endoscopic perforator vein surgery (SEPS) for chronic venous insufficiency. *Phlebology* 2009;**24**(1):8-16.

Lurie 2003

Lurie F, Creton D, Eklof B, Kabnick LS, Kistner RL, Pichot O, et al. Prospective randomized study of endovenous radiofrequency obliteration (closure procedure) versus ligation and stripping in a selected patient population (EVOLVeS Study). *Journal of Vascular Surgery* 2003;**38**:207-14.

Margolis 2002

Margolis DJ, Bilker W, Santanna J, Baumgarten M. Venous leg ulcer: incidence and prevalence in the elderly. *Journal of the American Academy of Dermatology* 2002;**46**(3):381-6.

Mauck 2014

Mauck KF, Asi N, Undavalli C, Elraiyah TA, Nabhan M, Altayar O, et al. Systematic review and meta-analysis of surgical interventions versus conservative therapy for venous ulcers. *Journal of Vascular Surgery* 2014;**60**:60S-70S.

McDaniel 2002

McDaniel HB, Marston WA, Farber MA, Mendes RR, Owens LV, Young ML, et al. Recurrence of chronic venous ulcers on the basis of clinical, etiologic, anatomic, and pathophysiologic criteria and air plethysmography. *Journal of Vascular Surgery* 2002;**35**(4):723-8.

Moffatt 2007

Moffatt C, Martin R, Smithdale R. Leg Ulcer Management. Oxford: Blackwell Publishing, 2007.

Nelson 2014

Nelson EA, Bell-Syer SE. Compression for preventing recurrence of venous ulcers. *Cochrane Database of Systematic Reviews* 2014, Issue 9. [DOI: 10.1002/14651858.CD002303.pub3]

O'Donnell 2011

O'Donnell TF, Balk EM. The need for an intersociety consensus guideline for venous ulcer. *Journal of Vascular Surgery* 2011;**54**(6 Suppl):83S-90S.

O'Donnell 2014

O'Donnell TF, Passman MA, Marston WA, Ennis WJ, Dalsing M, Kistner RL, et al. Management of venous leg ulcers: clinical practice guidelines of the Society for Vascular Surgery® and the American Venous Forum. *Journal of Vascular Surgery* 2014;**60**(2 Suppl):3S-59S.

O'Meara 2012

O'Meara S, Cullum N, Nelson EA, Dumville JC. Compression for venous leg ulcers. *Cochrane Database of Systematic Reviews* 2012, Issue 11. [DOI: 10.1002/14651858.CD000265.pub3]

Olin 1999

Olin JW, Beusterien KM, Childs MB, Seavey C, McHugh L, Griffiths RI. Medical costs of treating venous stasis ulcers: evidence from a retrospective cohort study. *Vascular Medicine* 1999;**4**:1-7.

Padberg 2001

Padberg F. The physiology and hemodynamics of the normal venous circulation. In: Gloviczki P, Yao JS editor(s). Handbook of Venous Disorders. 2nd Edition. London: Arnold, 2001:25-35.

Parmar 1998

Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Statistics in Medicine* 1998;**17**:2815-34.

Passman 2010

Passman M, Elias S, Gloviczki M. Non-medical initiatives to decrease venous ulcers prevalence. *Journal of Vascular Surgery* 2010;**52**(5):29S-36S.

Patel 2006

Patel NP, Labropoulos N, Pappas PJ. Current management of venous ulceration. *Plastic and Reconstructive Surgery* 2006;**117**(7 Suppl):254S-60S.

Persoon 2004

Persoon A, Heinen MM, Van der Vleuten CJ, De Rooij MJ, Van de Kerkhof PC, Van Achterberg T. Leg ulcers: a review of their impact on daily life. *Journal of Clinical Nursing* 2004;**13**(3):341-54.

Price 2000

Price P, Harding K. Acute and chronic wounds: differences in self-reported health-related quality of life. *Journal of Wound Care* 2000;**9**(2):93-5.

PRISMA 2009

Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *BMJ* 2009;**339**:b2535.

Productivity Commission 2005

Australian Government Productivity Commission. Economic Implications of an ageing Australia: research report 24 March 2005. www.pc.gov.au/inquiries/completed/ageing/report/ageing.pdf (accessed 12 December 2018).

Copyright © 2019 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

RevMan 2014 [Computer program]

Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager 5 (RevMan 5). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Rice 2014

Rice JB, Desai U, Cummings AK, Birnbaum HG, Skornicki M, Parsons N. Burden of venous leg ulcers in the United States. *Journal of Medical Economics* 2014;**17**(5):347-56.

Robertson 2008

Robertson L, Evans C, Fowkes FG. Epidemiology of chronic venous disease. *Phlebology* 2008;**23**(3):103-11.

Schünemann 2011a

Schünemann HJ, Oxman AD, Higgins JP, Vist GE, Glasziou P, Guyatt GH. Chapter 11: Presenting results and 'Summary of findings' tables. In: Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Schünemann 2011b

Schünemann HJ, Oxman AD, Vist GE, Higgins JP, Deeks JJ, Glasziou P, et al. Chapter 12: Interpreting results and drawing conclusions. In: Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

SIGN 2010

Scottish Intercollegiate Guidelines Network (SIGN). Management of chronic venous leg ulcers. National clinical guideline 120. August 2010. www.sign.ac.uk/sign-120-management-of-chronic-venous-leg-ulcers.html (accessed 6 November 2017).

SIGN 2018

Scottish Intercollegiate Guidelines Network (SIGN). Search filters. www.sign.ac.uk/search-filters.html (accessed 12 December 2018).

Soares 2009

Soares MO, Iglesias CP, Bland JM, Cullum N, Dumville JC, Nelson EA, et al. VenUS II team. Cost effectiveness analysis of larval therapy for leg ulcers. *BMJ* 2009;**338**:b825.

Stacey 2001

Stacey M. Investigation and treatment of chronic venous ulcer disease. *ANZ Journal of Surgery* 2001;**71**(4):226-9.

Sterne 2011

Sterne JA, Egger M, Moher D, editor(s). Chapter 10: Addressing reporting biases. In: Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Sybrandy 2001

Sybrandy JE, Van Gent WB, Pierik EG, Wittens CH. Endoscopic versus open subfascial division of incompetent perforating veins in the treatment of venous leg ulceration: long-term follow-up. *Journal of Vascular Surgery* 2001;**33**(5):1028-32.

Tassiopoulos 2000

Tassiopoulos AK, Golts E, Oh S, Labropoulos N. Current concepts in chronic venous ulceration. *European Journal of Vascular and Endovascular Surgery* 2000;**20**(3):227-32.

Tenbrook 2004

Tenbrook JA, Iafrati MD, O'Donnell TF, Wolf MP, Hoffman SN, Pauker SG, et al. Systematic review of outcomes after surgical management of venous disease incorporating subfascial endoscopic perforator surgery. *Journal of Vascular Surgery* 2004;**39**(3):583-9.

Tierney 2007

Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials* 2007;**8**:16. [DOI: 10.1186/1745-6215-8-16]

Vowden 2006

Vowden KR, Vowden P. Preventing venous ulcer recurrence. *International Wound Journal* 2006;**3**(1):11-21.

Weller 2013a

Weller C. Compression improves healing of venous leg ulcers compared to no compression, with differences between different compression systems. *Evidence Based Nursing* 2013;**16**:94.

Weller 2013b

Weller C, Buchbinder R, Johnston RV. Interventions for helping people adhere to compression treatments for venous leg ulceration. *Cochrane Database of Systematic Reviews* 2013, Issue 9. [DOI: 10.1002/14651858.CD008378.pub2]

Wittens 2004

Wittens CH, Van Gent WB, Hop WC. Conservative versus surgical treatment of venous leg ulcers (Dutch SEPS trial). *Phlebology/ Venous Forum of the Royal Society of Medicine* 2004;**19**(3):157.

Wollina 2006

Wollina U, Abdel-Naser MB, Mani R. A review of the microcirculation in skin in patients with chronic venous insufficiency: the problem and the evidence available for therapeutic options. *International Journal of Lower Extremity Wounds* 2006;**5**(3):169-80.

References to other published versions of this review

Lin 2016

Lin ZC, Loveland PM, Johnston RV, Bruce M, Weller CD. Subfascial endoscopic perforator surgery (SEPS) for treating and preventing recurrence of venous leg ulcers. *Cochrane Database of Systematic Reviews* 2016, Issue 4. [DOI: 10.1002/14651858.CD012164]

* Indicates the major publication for the study

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Callini 2002

Methods	**Study design**: randomised controlled trial **Setting:** hospital **Single or multicentre:** single **Country:** Italy **Duration:** 18 months (no date published in study) **Randomisation process:** not reported **Sample size calculation**: not reported
Participants	**Inclusion criteria of study:** • ulcer present • incompetent deep and superficial perforator veins **Exclusion criteria of study:** not reported **SEPS plus compression:** Number of participants at enrolment: 6 Number randomised: 6 Number at follow-up: 6 **Compression therapy:** Number of participants at enrolment: 6 Number randomised: 6 Number at follow-up: 6 **Baseline characteristics:** Mean age of the 30 participants in the overall prospective trial was 59 years (range 41 to 78). No reports of gender, comorbidities, ulcer size and duration, number of ulcers, severity of ulcers as defined by trialists, associated pain, and quality of life
Interventions	**SEPS + compression therapy:** not clearly detailed in study, but refers to the use of subfascial endoscopic perforator surgery as described in the Description of the intervention section, in addition to the use of elastic compression stockings to aid venous return in participants' lower limbs **Compression therapy:** not clearly detailed in study, but refers in most instances to the use of elastic compression stockings to aid venous return in participants' lower limbs
Outcomes	**Primary outcomes:** recurrence: measured dichotomously as a proportion in each group at time point of 6 to 18 months **Outcomes included in this review:** recurrence **Outcomes not included in this review:** nil

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Callini 2002 *(Continued)*

Source of funding	No source of funding was reported.
Notes	No tables or figures included; text translated from Italian to English. There is no record of trial registration. It is unclear if adverse events were recorded.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported if assessor of ulcer recurrence was blinded, thus we assessed this study as at unclear risk of detection bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up noted.
Selective reporting (reporting bias)	High risk	No protocol published; data reporting is limited to outcomes that showed benefit; no adverse outcomes and no numerical data were reported.
Other bias	Unclear risk	No baseline data were reported. It was also unclear if co-interventions were applied equally.

Nelzen 2011

Methods	**Study design**: randomised controlled trial **Setting:** multiple community hospitals **Single or multicentre:** multicentre **Country:** Denmark and Sweden **Duration:** 12 months follow-up, duration of study was 6 years (January 2001 to April 2007) **Randomisation process:** sealed and numbered envelopes prepared in batches of 10, stratified according to centre and healed and active ulcer, and opened at time of surgery **Sample size calculation**: not reported **Follow-up:** duplex scan at 6 to 9 months after surgery; clinical follow-up was scheduled after 1 week, 3 and 12 months. A standard questionnaire was completed at each clinical visit.
Participants	**Inclusion criteria of study:** • ulcer must be present (open or healed) for a duration of at least 6 weeks

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Nelzen 2011 *(Continued)*

- duplex scan showing incompetence of the saphenous vein plus 1 or more medial lower leg incompetent perforators with a diameter greater than 2 mm
- CEAP clinical class C5 or C6
- ankle brachial pressure index at least 0.8
- age 30 to 78 years

Exclusion criteria of study:

- incompetence of the popliteal vein (isolated segmental incompetence of the femoral vein was allowed)
- severe cardiovascular disease
- malignancy
- renal failure
- expected survival less than 5 years
- dementia

Group 1: SEPS + saphenous surgery:

Number of participants at enrolment: 37

Number randomised: 37

Number at follow-up: 36

Age: median 57, range 35 to 78 years

Sex: M:F = 18:19

Diagnosis: CEAP C5 = 27, C6 = 10

Duration of symptoms:

- ulcer duration (months): 5 (range 1 to 42)
- total ulcer history (median, months): 12 (1 to 180)

Treatment history: previous varicose vein surgery: 8 (22%)

Concurrent treatment: some used compression postsurgery (no comment on pre-surgery or any more specific information)

Group 2: saphenous surgery only:

Number of participants at enrolment: 38

Number randomised: 38

Number at follow-up: 38

Age: median 61, range 28 to 78 years

Sex: M:F = 13:25

Diagnosis: CEAP C5 = 26, C6 = 12

Duration of symptoms:

- ulcer duration (months): 6 (1 to 24)
- total ulcer history (median, months): 10 (2 to 169)

Treatment history: previous varicose vein surgery: 7 (18%)

Concurrent treatment: some used compression postsurgery (no comment on pre-surgery or any more specific information)

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Nelzen 2011 *(Continued)*

	No reports of ulcer size, comorbidities, number of ulcers, severity of ulcers as defined by trialists, associated pain, and quality of life **Pre-treatment group differences:** • significantly more participants in the SEPS group had multiple episodes of ulceration compared than in the no SEPS group (20 of 37 vs 14 of 38; P = 0.005) • higher proportion of females in no SEPS group (F:M = 25:13 = 1:0.52) compared to the SEPS group (F:M = 19:18 = 1:0.95), not commented on by authors • no differences between the no SEPS and SEPS groups regarding duration of the last ulcer or total ulcer history
Interventions	**SEPS + saphenous surgery:** • SEPS performed after saphenous surgery within the same procedure (see description of saphenous surgery below) with one of the single-port instruments available at the time, performed in a bloodless field using a tourniquet. • incision for SEPS was located medially on the proximal calf and about 3 cm dorsal to the border of the tibia. The deep fascia in the lower third of the calf was incised routinely in order not to miss distal perforators. • all incompetent perforators located on the preoperative duplex scan were identified and interrupted either with clip ligation or by means of bipolar diathermy. Perforators were then preferably also divided. Wide (3 mm or more) perforators not previously identified as incompetent, or not previously detected, were divided, as well as smaller perforators if they hindered further progression of the operation. • routine division of all perforating veins encountered was not recommended. Division of very distal perforators was performed only if the anatomy was perfectly clear, to avoid damage to neurovascular structures. **Saphenous surgery (stripping of multiple veins):** • if incompetent, the great saphenous vein was divided flush with the femoral vein, with division of all proximal tributaries. Additional stripping was recommended down to, or below, the knee. • phlebectomies were done through stab incisions, avoiding the vicinity of known incompetent perforators and areas with lipodermatosclerosis. For small saphenous veins, ligation was carried out as close to the saphenopopliteal junction as possible, but not necessarily always flush, in order to avoid unnecessary nerve damage in the popliteal fossa. Partial stripping of the small saphenous veins was optional. • redo surgery for remnant great saphenous vein was done by a medial or lateral approach to the femoral vein to locate the saphenofemoral junction. Residual great saphenous vein or accessory veins were removed according to the same principles as for primary surgery. **[Comparator(s)] saphenous surgery alone:** Description: as above for saphenous surgery section **Co-interventions:** compression therapy **Any additional treatment during trial (for all groups):** some used compression postsurgery (no comment on pre-surgery or any more specific information about type, prevalence, or adherence); no other co-interventions mentioned
Outcomes	**Primary outcomes:** • venous ulcer healing proportion: measured as a proportion of each group at 12 months • time to complete healing: measured as a continuous outcome, excluding ulcers that did not heal at 12-month follow-up • recurrence of venous ulcer: measured as a proportion of each group at 12 months • adverse events: measured as a dichotomous outcome and reported qualitatively at 30 days • overall measures of venous function: measured with a duplex scan, and with continuous outcomes of how many incompetent perforators remained at 6 to 9 months

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Nelzen 2011 *(Continued)*

- patient satisfaction: measured on a rating scale of severe, some, minor, and no symptoms at 3 and 12 months and compared to pre-surgery

Outcomes included in this review:

- proportion of ulcers healed
- ulcer recurrence
- ulcer healing time
- adverse events

Source of funding	General research grant from the Skaraborg Hospital Research & Development Fund No conflict of interest known.
Notes	There is no record of trial registration **Adverse events:** SEPS group out of 37: wound infection (6), delayed wound healing (3), pain (6), swelling (1), DVT (0) No SEPS group out of 38: wound infection (3), delayed wound healing (1), pain (1), swelling (1), DVT (0)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation took place in the operating theatre; it appears the sequence was generated centrally, and although unclearly reported, this was likely to be adequate.
Allocation concealment (selection bias)	Low risk	Sealed and numbered envelopes prepared in batches of 10 and stratified according to centre and healed or active ulcer, opened at time of surgery
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants were blinded, but surgeons/investigators were not.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Surgeons and nurses were not blinded. Assessor of wound healing was blinded. Duplex technicians were blinded – relevant only for venous ejection/Doppler outcomes.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Participants lost to follow-up: it was not stated if the 1 participant lost to follow-up in SEPS group was C5 or C6 ulcer, or why they were lost to follow-up; also 1 participant in the SEPS group was not included in outcome analysis of time points other than 12 months. Overall, this is a small proportion of the cohort and is essentially balanced between groups.
Selective reporting (reporting bias)	High risk	Ulcer healing and recurrence at time points other that 12 months is not reported, and specifics regarding recurrence are somewhat unclear (i.e. was it C5 ulcer or healed C6 ulcers that recurred). Symptoms are not reported separately for groups, just overall postoperatively; ejection fractions or volumes not reported; complications reported only for first 30 days postoperatively.
Other bias	Low risk	General research grant from the Skaraborg Hospital Research and Development Fund. The authors declare no conflict of interest.

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Pierik 1997

Methods	**Study design**: randomised controlled trial **Setting:** hospital **Single or multicentre**: multicentre (3) **Country:** Netherlands **Duration:** 15-month recruitment period, 60-month follow-up (February 1994 to 1999 (recruitment ended in April 1995)) **Randomisation process:** participants were randomly allocated to either open or endoscopic surgery by opening sealed envelopes. Participants were stratified for the presence or absence of superficial venous incompetence for primary or recurrent ulceration and for the presence of diabetes mellitus. **Sample size calculation:** not reported **Follow-up:** 60 months follow-up for duplex ultrasonography, healing of ulcers, and recurrence
Participants	**Inclusion criteria of study:** • all participants with current venous ulceration on the medial aspect of the lower leg (CEAP C6) • all participants underwent physical examination and duplex ultrasound scan before the operation and 6 weeks afterward **Exclusion criteria of study:** • ankle brachial pressure index less than 0.8 • previous surgical subfascial exploration **Group 1: endoscopic approach (SEPS)** Number of participants at enrolment: 20 Number randomised: 20 Number at follow-up: 19 Age: mean 64, range 33 to 89 years Sex: M:F = 9:11 Diagnosis: recurrent ulcer: 13 Ulcer size: mean 9 cm^2, range 3 to 28 cm^2 Duration of symptoms: mean 299 days, range 20 to 3650 days Duration of ulceration: mean 148 months, range 11 to 600 months Concurrent treatment: mobilisation, ambulant compression therapy **Group 2: open approach (Linton procedure)** Number of participants at enrolment: 19 Number randomised: 19 Number at follow-up: 18 Age: mean 70, range 36 to 89 years Sex: M:F = 3:16

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Pierik 1997 *(Continued)*

Diagnosis: recurrent ulcer: 12

Ulcer size: mean 11 cm^2, range 3 to 30 cm^2

Duration of symptoms: mean 249 days, range 14 to 1825 days

Duration of ulceration: mean 140 days, range 9 to 480 months

Concurrent treatment: mobilisation, ambulant compression therapy

No reports of comorbidities, number of ulcers, severity of ulcers as defined by trialists, associated pain, and quality of life.

Pre-treatment group differences:

Predominance of women in the open (comparator) group compared with the SEPS (intervention) group

The number and distribution of incompetent perforating veins were comparable in both groups.

The mean number of perforating veins found at operation was the same for both groups (3.0 vs 2.9).

Interventions	**SEPS:** • performed by "skilled surgeons" who had performed more than 10 of the procedures prior. • mediastinoscope was used without a thigh tourniquet. • all perforating veins on the medial and dorsal side of the lower leg that could be found were interrupted by the use of hemoclips (Ligaclip, Ethicon Endosurgery, Johnson & Johnson, USA) and divided. At the end of the operation, the deep fascia was left open and the skin was closed by staples. • participants were mobilised on the first postoperative day and were treated by ambulant compression therapy (Comprilan, Beiersdorf Medical, the Netherlands) until the ulcer had healed. Elastic stockings (Elvarex, Beiersdorf Medical) were prescribed indefinitely when associated deep venous incompetence was present. **Modified Linton approach** (open subfascial exploration): • performed by "skilled surgeons" who had performed more than 10 of the procedures prior. • incision on the medial side of the lower leg down from the level of Boyd's perforator to the medial malleolus was made through the fascia. • all perforating veins on the medial and dorsal side of the lower leg that could be found were interrupted by the use of hemoclips (Ligaclip, Ethicon Endosurgery, Johnson & Johnson, USA) and divided. At the end of the operation, the deep fascia was left open and the skin was closed by staples. • participants were mobilised on the first postoperative day and were treated by ambulant compression therapy (Comprilan, Beiersdorf Medical, the Netherlands) until the ulcer had healed. Elastic stockings (Elvarex, Beiersdorf Medical) were prescribed indefinitely when associated deep venous incompetence was present. **Co-interventions:** any additional treatment during trial (for all groups): • all participants received 1.5 g cefuroxime by intravenous injection before the operation. • surgical: concomitant superficial venous incompetence was treated by flush saphenofemoral ligation and limited stripping of the long saphenous vein from groin to just below knee level. • compression: ambulant compression therapy (Comprilan, Beiersdorf Medical, the Netherlands) until the ulcer had healed. Elastic stockings (Elvarex, Beiersdorf Medical) were prescribed indefinitely when associated deep venous incompetence was present. None of the participants underwent a second operative ligation of perforating veins or flush ligation and stripping of the long or short saphenous vein after the initial operation. Sclerotherapy was not performed in any of the participants during follow-up.
Outcomes	**Primary outcomes:** • venous ulcer healing proportion: measured as a proportion of each group at 6, 12, 24, and 36 months

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Pierik 1997 *(Continued)*

- recurrence of venous ulcer: measured as a proportion of each group at 60 months
- adverse events: measured as a dichotomous outcome during the inpatient stay
- overall measures of venous function: measured with a duplex scan, and with continuous outcomes of how many incompetent perforators remained at 6 to 9 months
- readmission rate: as a proportion of the group
- hospital stay: as a continuous outcome for each group

Outcomes included in this review:

- proportion of ulcers healed
- ulcer recurrence
- adverse events
- serious adverse events

Source of funding	No source of funding was reported.

Notes	• Unscheduled interim analysis was performed at 15 months (April 1995) due to concerns about high incidence of wound complications. As there was a statistically significant increased risk of infection with the open (Linton) procedure, recruitment to the trial was halted early.
	• Additional adverse events during follow-up: there was limited reporting of adverse events during follow-up.
	  ○ SEPS: no participants were readmitted for reoperation/intravenous antibiotics, 1 died of a myocardial infarction 5 months post operation.
	  ○ Linton: 2 participants were readmitted for reoperation/intravenous antibiotics, nil other adverse events noted.
	• Initial power calculations indicated that 47 participants would need to be included in each group (with expected wound complication rates of 40% for open and 10% for endoscopic perforantectomy), which evidently could not be met.
	• Mean blood loss was 170 mL in the open group and 43 mL in the endoscopic group.
	• Mean hospital stay was 3 days shorter in the endoscopic group than in the open group (3 days vs 7 days; P = 0.001).
	• Data on interventions extracted for this review, study also includes baseline characteristics for circumference of ulcer, total duration of ulcer, duration of present ulcer, and preoperative duplex findings (superficial incompetence vs deep incompetence vs incompetent perforating veins).
	• Time points extracted for this review: participants returned to the outpatient clinic at 1, 2, 6, 12, 24, and 52 weeks and 48 months after surgery.
	• There is no record of trial registration.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation was not reported.
Allocation concealment (selection bias)	Unclear risk	Participants were randomly allocated to either open or endoscopic surgery by "opening sealed envelopes", but it was unclear if the envelopes were in sequential order, opaque, or if the sequence in the envelope was truly random or in alternate order.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No mention of blinding – likely not attempted as type of intervention received would have been obvious.
Blinding of outcome assessment (detection bias)	Unclear risk	Not reported if assessor of ulcer healing was blinded, thus unclear risk of detection bias

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Pierik 1997 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "follow-up was complete in all patients, with the exception of two patients (1 in each group) ... during a follow-up period of 5 years (mean follow-up period in the Linton group, 50.6 months; mean follow-up period in the SEPS group, 46.1 months), four patients (all in the SEPS group) died of causes other than venous leg ulceration. A below-knee amputation was performed in one patient in the SEPS group, because of a squamous cell carcinoma that had developed in the venous ulcer…This could explain the 5½-month, not statistically significant, difference in the follow-up periods between the two groups" Comment: small proportion, and this is accounted for and described by authors
Selective reporting (reporting bias)	Unclear risk	There was no published protocol. The trial was stopped after adverse events occurred in both groups, however outcomes introduced appeared to have been reported.
Other bias	Unclear risk	Funding source not disclosed, no conflicts of interest (or lack thereof) reported.

Van Gent 2006

Methods	**Study design**: prospective randomised controlled trial **Setting:** hospital **Single or multicentre:** multicentre (12) **Country:** Netherlands **Duration:** data collected April 1997 to January 2001 **Randomisation process:** stratified before randomisation for 3 factors: first-time ulcer or recurrent ulceration; presence or absence of DVI; and centre For allocation to the treatment groups, each participant was assigned by a computer program at an independent randomisation centre. The randomisation took place within stratification groups. In case participants had 2 ulcerated legs in the study, the legs were randomised separately. **Sample size calculation:** not reported **Follow-up:** up to 29 months, healing of ulcers, and recurrence
Participants	**Inclusion criteria of study:** • active (open) venous leg ulcer (CEAP C6), • medial and lateral locations • bilateral leg ulcers accepted **Exclusion criteria of study:** • arterial pathology (ankle-brachial index < 0.8) • total or partial occlusion of the deep venous system • former subfascial ligation of perforating veins • severe neurologic or muscular pathology • immobility **SEPS and compression therapy:**

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Van Gent 2006 *(Continued)*

	Number of participants at enrolment: 97 legs Number randomised: 97 legs Number included in analyses: 94 legs Age: mean 64 years, range 49 to 79 years Sex: M:F = 2:3 Ulcer size: median 225 mm^2, range 4 to 7800 mm^2 Ulcer location: 74% medial **Compression therapy alone:** Number of participants at enrolment: 103 legs Number randomised: 103 legs Number included in analyses: 102 legs (1 lost to follow-up) Age: mean 68 years, range 54 to 82 years Sex: M:F = 2:3 Ulcer size: median 260 mm^2, range 1 to 27,000 mm^{2a} Ulcer location: 61% medial No reports of comorbidities, ulcer duration, number of ulcers, severity of ulcers as defined by trialists, associated pain, and quality of life **Pre-treatment group differences:** Diabetes mellitus: 17 (17%) conservative group, 6 (7%) in surgical group (P = 0.05) No difference in sex, age, first-time ulcer, deep vein incompetence, previous DVT, localisation of ulcer, or ulcer size
Interventions	**SEPS and compression therapy** **SEPS:** • 1-port technique and carbon dioxide were used in all cases. All perforating veins were interrupted by the use of hemoclips (Ligaclip, Ethicon Endosurgery Amersfoort, the Netherlands) in a bloodless area. • intermuscular septum was opened to reach perforators near the tibial crest in the lower part of the leg. • participants were mobilised on the first postoperative day and treated by dual-layer short-stretch ambulatory compression therapy (Comprilan, Beiersdorf Medical, Almere, the Netherlands) until the ulcer had healed. • therapeutic elastic stockings (class II or III, depending on concomitant incompetence of the deep vein system) were prescribed. **Compression therapy only:** • standardised ambulatory compression therapy; therapeutic elastic stockings.
Outcomes	**Primary outcomes:** • venous ulcer healing rate: measured as a proportion of each group at 6, 12, and 24 months • recurrence of venous ulcer: measured as a proportion of each group at 6, 12, 24, and beyond 24 months (as per follow-up) • mean and median time to ulcer healing (11 and 4.2 months in the surgical group and 15 and 5.7 months in the conservative group)

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Van Gent 2006 *(Continued)*

	Outcomes included in this review: • ulcer healing rate • ulcer recurrence
Source of funding	The study was sponsored by Ziekenfondsraad/Ontwikkelingsgeneeskunde (Dutch government; project OG98-045). The sponsor of the study had no role in data collection, data analysis, data interpretation, writing the report, or the decision to submit the paper for publication.
Notes	There is no record of trial registration. It is unclear if adverse events were reported in the trial.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "for allocation to the treatment groups, each patient was assigned by a computer program at an independent randomisation center. The randomisation took place within stratification groups. In case patients had two ulcerated legs in the study, the legs were randomised separately"
Allocation concealment (selection bias)	Low risk	Quote: "stratified before randomisation for three factors: first-time ulcer or recurrent ulceration; presence or absence of DVI; and center… each patient was assigned by a computer program at an independent randomisation center"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unable to blind participants, as 1 group had compression bandaging and the other had surgery and compression bandaging; likely to be confounded by performance bias
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unable to blind the outcome assessment due to the associated surgical scars when examining the venous ulcers during intervals after treatment. Not reported if assessor of ulcer healing was blinded, thus we judged the risk of bias as unclear
Incomplete outcome data (attrition bias) All outcomes	Low risk	Surgery + compression group: 3 of 97 randomised legs lost to follow-up within 1 month, a further 3 did not undergo surgery, but all 94 were analysed Compression-only group: 1 of 102 legs lost to follow-up within 1 month. 102 legs analysed. 4 legs lost to follow-up within the first month were not analysed; overall this is a small percentage of the total study population.
Selective reporting (reporting bias)	Unclear risk	All outcomes reported as planned in methods; no published protocol and no reporting of adverse events.
Other bias	Low risk	Funded by the Dutch Government, no role in data collection/analysis or publication

[a] Review authors think this is an error but have not confirmed this with study authors.
CEAP: classification of venous disorders based on their clinical, etiologic, anatomic, and pathophysiologic (CEAP) characteristics
DVI: deep venous insufficiency
DVT: deep vein thrombosis
SEPS: subfascial endoscopic perforator vein surgery

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Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Gan 2013	Comparator was SEPS + EVLT vs no treatment; unable to isolate the effect of SEPS alone.
Gloviczki 1999	Systematic review, not an RCT
Gloviczki 2000	Not an RCT
Jeanneret 2003	Not an RCT
Sharma 2011	Did not examine the effect on venous leg ulcers, only varicose veins
Taradaj 2011	Intervention was not SEPS.
Wang 2009	Comparison of 2 different areas of SEPS application, could not isolate the effects of SEPS alone
Warburg 1994	Intervention was not SEPS.

EVLT: endovenous laser therapy
RCT: randomised controlled trial
SEPS: subfascial endoscopic perforator vein surgery

DATA AND ANALYSES

Comparison 1. SEPS + compression therapy versus compression therapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion of ulcers healed	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 0 to 6 months	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 6 to 12 months	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.3 12 to 24 months	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Ulcer recurrence	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 0 to 6 months	1	196	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.27, 1.41]
2.2 6 to 12 months	1	196	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.37, 1.42]
2.3 12 to 24 months	2	208	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.26, 2.76]

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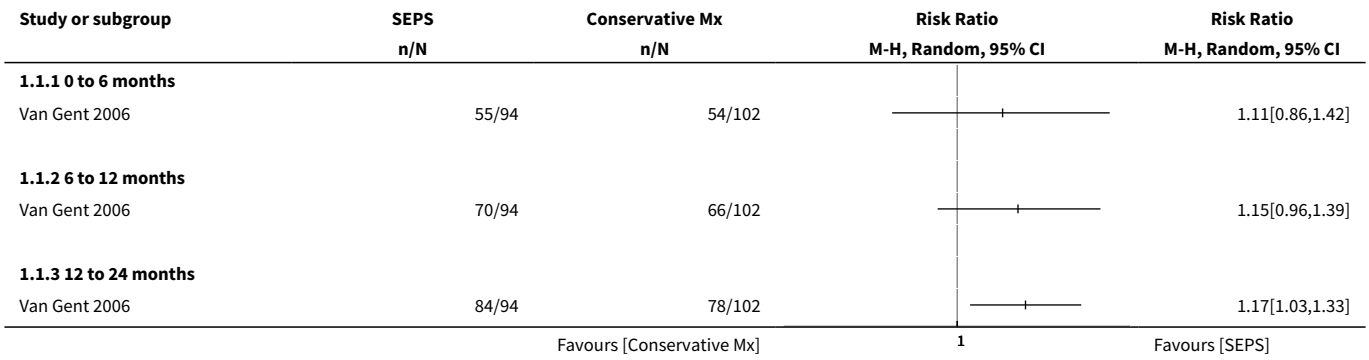
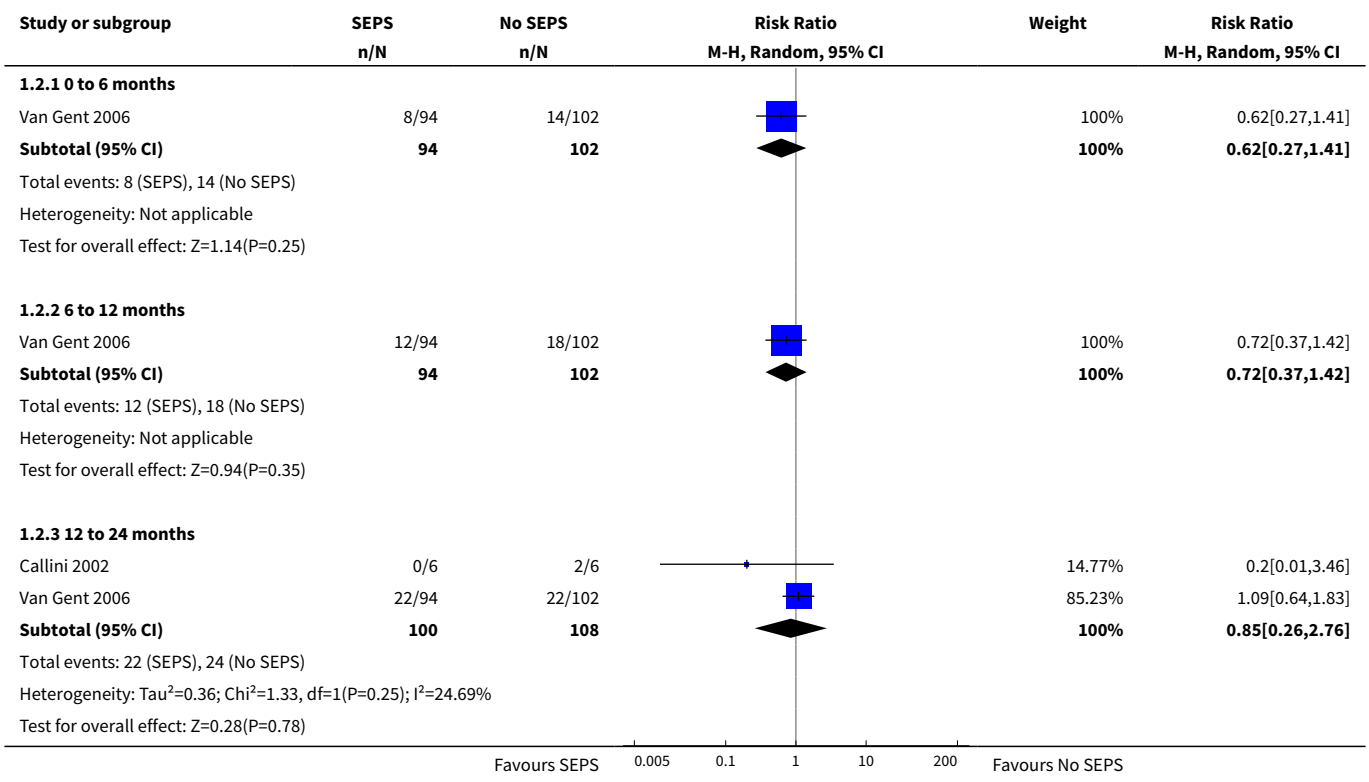
Analysis 1.1. Comparison 1 SEPS + compression therapy versus compression therapy, Outcome 1 Proportion of ulcers healed.



Analysis 1.2. Comparison 1 SEPS + compression therapy versus compression therapy, Outcome 2 Ulcer recurrence.



Comparison 2. SEPS versus the Linton procedure

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion of ulcers healed	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

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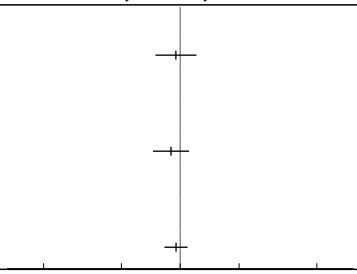
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 0 to 6 months	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 6 to 12 months	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.3 12 to 24 months	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Ulcer recurrence (60 months)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

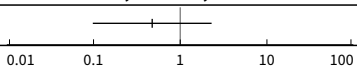
Analysis 2.1. Comparison 2 SEPS versus the Linton procedure, Outcome 1 Proportion of ulcers healed.

Study or subgroup	SEPS n/N	Linton n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
2.1.1 0 to 6 months				
Pierik 1997	17/20	17/19		0.95[0.75,1.21]
2.1.2 6 to 12 months				
Pierik 1997	17/20	18/19		0.9[0.73,1.11]
2.1.3 12 to 24 months				
Pierik 1997	19/20	19/19		0.95[0.83,1.09]



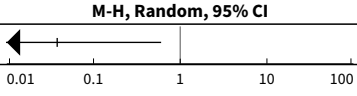
Analysis 2.2. Comparison 2 SEPS versus the Linton procedure, Outcome 2 Ulcer recurrence (60 months).

Study or subgroup	SEPS n/N	Linton n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Pierik 1997	2/20	4/19		0.48[0.1,2.3]



Analysis 2.3. Comparison 2 SEPS versus the Linton procedure, Outcome 3 Adverse events.

Study or subgroup	SEPS n/N	Linton n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Pierik 1997	0/20	12/19		0.04[0,0.6]



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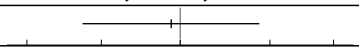
Comparison 3. SEPS + saphenous surgery versus saphenous surgery

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion of ulcers healed (12 months)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Ulcer recurrence	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 6 months	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 12 months	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

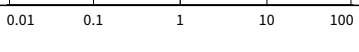
Analysis 3.1. Comparison 3 SEPS + saphenous surgery versus saphenous surgery, Outcome 1 Proportion of ulcers healed (12 months).

Study or subgroup	SEPS + saphenous surgery n/N	Saphenous Surgery n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Nelzen 2011	8/10	10/12		0.96[0.64,1.43]



Analysis 3.2. Comparison 3 SEPS + saphenous surgery versus saphenous surgery, Outcome 2 Ulcer recurrence.

Study or subgroup	SEPS + Saphenous Surgery n/N	Saphenous Surgery n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
3.2.1 6 months				
Nelzen 2011	4/37	4/38		1.03[0.28,3.81]
3.2.2 12 months				
Nelzen 2011	2/37	2/38		1.03[0.15,6.91]



Analysis 3.3. Comparison 3 SEPS + saphenous surgery versus saphenous surgery, Outcome 3 Adverse events.

Study or subgroup	SEPS + saphenous surgery n/N	Saphenous surgery n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Nelzen 2011	12/37	6/38		2.05[0.86,4.9]

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APPENDICES

Appendix 1. Search strategies

Cochrane Wounds Specialised Register

1 MESH DESCRIPTOR Leg Ulcer EXPLODE ALL AND INREGISTER
2 ((varicose next ulcer*) or (venous next ulcer*) or (leg next ulcer*) or (foot next ulcer*) or (stasis next ulcer*) or (lower next extremit* near2 ulcer*) or (crural next ulcer*) or "ulcus cruris" or "ulcer cruris") AND INREGISTER
3 #1 OR #2
4 MESH DESCRIPTOR Minimally Invasive Surgical Procedures EXPLODE ALL AND INREGISTER
5 MESH DESCRIPTOR Endovascular Procedures EXPLODE ALL AND INREGISTER
6 MESH DESCRIPTOR Endoscopy EXPLODE ALL AND INREGISTER
7 MESH DESCRIPTOR Angioscopy EXPLODE ALL AND INREGISTER
8 MESH DESCRIPTOR Vascular Surgical Procedures EXPLODE ALL AND INREGISTER
9 MESH DESCRIPTOR Saphenous Vein EXPLODE ALL WITH QUALIFIER SU AND INREGISTER
10 MESH DESCRIPTOR Veins EXPLODE ALL WITH QUALIFIER SU AND INREGISTER
11 MESH DESCRIPTOR Leg EXPLODE ALL AND INREGISTER
12 #10 AND #11
13 #12 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9
14 (endoscop* and (surger* or surgic* or ligation* or ligatur* or ablation*)) AND INREGISTER
15 ((endoscop* or subfascial) and perforat*) AND INREGISTER
16 SEPS AND INREGISTER
17 #13 OR #14 OR #15 OR #16
18 #17 AND #3

The Cochrane Central Register of Controlled Clinical Trials (CENTRAL)

#1 MeSH descriptor: [Leg Ulcer] explode all trees
#2 ((varicose next ulcer*) or (venous next ulcer*) or (leg next ulcer*) or (foot next ulcer*) or (stasis next ulcer*) or (lower next extremit* near/2 ulcer*) or (crural next ulcer*) or "ulcus cruris" or "ulcer cruris"):ti,ab,kw
#3 {or #1-#2}
#4 MeSH descriptor: [Minimally Invasive Surgical Procedures] this term only
#5 MeSH descriptor: [Endovascular Procedures] this term only
#6 MeSH descriptor: [Endoscopy] explode all trees
#7 MeSH descriptor: [Angioscopy] explode all trees
#8 MeSH descriptor: [Vascular Surgical Procedures] this term only
#9 MeSH descriptor: [Saphenous Vein] this term only and with qualifier(s): [Surgery - SU]
#10 MeSH descriptor: [Veins] this term only and with qualifier(s): [Surgery - SU]
#11 MeSH descriptor: [Leg] explode all trees
#12 {and #10-#11}
#13 (endoscop* and (surger* or surgic* or ligation* or ligatur* or ablation*)):ti,ab,kw
#14 ((endoscop* or subfascial) and perforat*):ti,ab,kw
#15 SEPS:ti,ab
#16 {or #4-#9, #12-#15}
#17 {and #3, #16} in Trials

Ovid MEDLINE

1 exp Leg Ulcer/
2 ((varicose adj ulcer*) or (venous adj ulcer*) or (leg adj ulcer*) or (foot adj ulcer*) or (stasis adj ulcer*) or (lower adj extremit* adj2 ulcer*) or (crural adj ulcer*) or "ulcus cruris" or "ulcer cruris").tw.
3 or/1-2
4 Minimally Invasive Surgical Procedures/
5 Endovascular Procedures/
6 exp Endoscopy/
7 exp Angioscopy/
8 Vascular Surgical Procedures/
9 Saphenous Vein/su [Surgery]
10 Veins/su and Leg/
11 (endoscop* and (surger* or surgic* or ligation* or ligatur* or ablation*)).ti,ab.
12 ((endoscop* or subfascial) and perforat*).ti,ab.
13 SEPS.ti,ab.

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14 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15 3 and 14
16 randomised controlled trial.pt.
17 controlled clinical trial.pt.
18 randomi?ed.ab.
19 placebo.ab.
20 clinical trials as topic.sh.
21 randomly.ab.
22 trial.ti.
23 or/16-22
24 exp animals/ not humans.sh.
25 23 not 24
26 15 and 25

Ovid Embase

1 exp leg ulcer/
2 ((varicose adj ulcer*) or (venous adj ulcer*) or (leg adj ulcer*) or (foot adj ulcer*) or (stasis adj ulcer*) or (lower adj extremit* adj2 ulcer*) or (crural adj ulcer*) or "ulcus cruris" or "ulcer cruris").tw.
3 or/1-2
4 exp minimally invasive surgery/
5 endovascular surgery/
6 vein surgery/
7 vascular surgery/
8 exp endoscopy/
9 exp angioscopy/
10 saphenous vein/su [Surgery]
11 vein/su and leg/
12 (endoscop* and (surger* or surgic* or ligation* or ligatur* or ablation*)).ti,ab.
13 ((endoscop* or subfascial) and perforat*).ti,ab.
14 SEPS.ti,ab.
15 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16 3 and 15
17 Randomized controlled trials/
18 Single-Blind Method/
19 Double-Blind Method/
20 Crossover Procedure/
21 (random* or factorial* or crossover* or cross over* or cross-over* or placebo* or assign* or allocat* or volunteer*).ti,ab.
22 (doubl* adj blind*).ti,ab.
23 (singl* adj blind*).ti,ab.
24 or/17-23
25 exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/
26 human/ or human cell/
27 and/25-26
28 25 not 27
29 24 not 28
30 16 and 29

EBSCO CINAHL Plus

S29 S15 AND S28
S28 S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27
S27 TI allocat* random* or AB allocat* random*
S26 MH "Quantitative Studies"
S25 TI placebo* or AB placebo*
S24 MH "Placebos"
S23 TI random* allocat* or AB random* allocat*
S22 MH "Random Assignment"
S21 TI randomi?ed control* trial* or AB randomi?ed control* trial*
S20 AB (singl* or doubl* or trebl* or tripl*) and AB (blind* or mask*)
S19 TI (singl* or doubl* or trebl* or tripl*) and TI (blind* or mask*)
S18 TI clinic* N1 trial* or AB clinic* N1 trial*
S17 PT Clinical trial

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S16 MH "Clinical Trials+"
S15 S3 AND S14
S14 S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13
S13 TX SEPS
S12 TX ((endoscop* or subfascial) and perforat*)
S11 TX (endoscop* and (surger* or surgic* or ligation* or ligatur* or ablation*))
S10 (MH "Veins/SU") AND (MH "Leg")
S9 (MH "Saphenous Vein/SU")
S8 (MH "Venous Cutdown")
S7 (MH "Angioscopy")
S6 (MH "Endoscopy+")
S5 (MH "Vascular Surgery")
S4 (MH "Minimally Invasive Procedures")
S3 S1 OR S2
S2 TX ((varicose N1 ulcer*) or (venous N1 ulcer*) or (leg N1 ulcer*) or (foot N1 ulcer*) or (stasis N1 ulcer*) or ((lower N1 extremit*) N2 ulcer*) or (crural N1 ulcer*) or "ulcus cruris" or "ulcer cruris")
S1 (MH "Leg Ulcer+")

US National Institutes of Health Ongoing Trials Register (ClinicalTrials.gov)

Keywords: venous ulcer; leg ulcer; venous stasis; perforator veins; subfascial endoscopic perforator surgery; venous surgery; endoscopic venous surgery.

World Health Organization International Clinical Trials Registry Platform

Keywords: venous ulcer; leg ulcer; venous stasis; perforator veins; subfascial endoscopic perforator surgery; venous surgery; endoscopic venous surgery.

EU Clinical Trials Register (Clinicaltrialsregister.eu)

Keywords: venous ulcer; leg ulcer; venous stasis; perforator veins; subfascial endoscopic perforator surgery; venous surgery; endoscopic venous surgery.

Appendix 2. Risk of bias assessment

1. Was the allocation sequence randomly generated?

Low risk of bias

The investigators describe a random component in the sequence generation process such as: referring to a random number table; using a computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots.

High risk of bias

The investigators describe a non-random component in the sequence generation process. Usually, the description would involve some systematic, non-random approach, for example: sequence generated by odd or even date of birth; sequence generated by some rule based on date (or day) of admission; sequence generated by some rule based on hospital or clinic record number.

Unclear

Insufficient information about the sequence generation process to permit judgement of low or high risk of bias.

2. Was the treatment allocation adequately concealed?

Low risk of bias

Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: central allocation (including telephone, web-based and pharmacy-controlled randomisation); sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes.

High risk of bias

Participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on: use of an open random allocation schedule (e.g. a list of random numbers); assignment envelopes without appropriate safeguards (e.g. envelopes were unsealed, non-opaque, or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.

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Unclear

Insufficient information to permit judgement of low or high risk of bias. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement, for example if the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, opaque and sealed.

3. Blinding - was knowledge of the allocated interventions adequately prevented during the study?

Low risk of bias

Any one of the following.

- No blinding, but the review authors judge that the outcome and the outcome measurement are not likely to be influenced by lack of blinding.
- Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
- Either participants or some key study personnel were not blinded, but outcome assessment was blinded and the non-blinding of others unlikely to introduce bias.

High risk of bias

Any one of the following.

- No blinding or incomplete blinding, and the outcome or outcome measurement is likely to be influenced by lack of blinding.
- Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken.
- Either participants or some key study personnel were not blinded, and the non-blinding of others likely to introduce bias.

Unclear

Either of the following.

- Insufficient information to permit judgement of low or high risk of bias.
- The study did not address this outcome.

4. Were incomplete outcome data adequately addressed?

Low risk of bias

Any one of the following.

- No missing outcome data.
- Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias).
- Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups.
- For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate.
- For continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size.
- Missing data have been imputed using appropriate methods.

High risk of bias

Any one of the following.

- Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups.
- For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate.
- For continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size.
- 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation.
- Potentially inappropriate application of simple imputation.

Unclear

Either of the following.

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- Insufficient reporting of attrition/exclusions to permit judgement of low or high risk of bias (e.g. number randomised not stated, no reasons for missing data provided).
- The study did not address this outcome.

5. Are reports of the study free of suggestion of selective outcome reporting?

Low risk of bias

Either of the following.

- The study protocol is available and all of the study's prespecified (primary and secondary) outcomes that are of interest in the review have been reported in the prespecified way.
- The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were prespecified (convincing text of this nature may be uncommon).

High risk of bias

Any one of the following.

- Not all of the study's prespecified primary outcomes have been reported.
- One or more primary outcomes are reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not prespecified.
- One or more reported primary outcomes were not prespecified (unless clear justification for their reporting is provided, such as an unexpected adverse effect).
- One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis.
- The study report fails to include results for a key outcome that would be expected to have been reported for such a study.

Unclear

Insufficient information to permit judgement of low or high risk of bias. It is likely that the majority of studies will fall into this category.

6. Other sources of potential bias

Low risk of bias

The study appears to be free of other sources of bias.

High risk of bias

There is at least one important risk of bias. For example, the study:

- had a potential source of bias related to the specific study design used; or
- has been claimed to have been fraudulent; or
- had some other problem.

Unclear

There may be a risk of bias, but there is either:

- insufficient information to assess whether an important risk of bias exists; or
- insufficient rationale or evidence that an identified problem will introduce bias.

3 Risk of bias assessment (cluster-randomised controlled trials)

In cluster-randomised trials, particular biases to consider include: (i) recruitment bias; (ii) baseline imbalance; (iii) loss of clusters; (iv) incorrect analysis; and (v) comparability with individually randomised trials.

(i) Recruitment bias can occur when individuals are recruited to the trial after the clusters have been randomised, as the knowledge of whether each cluster is an 'intervention' or 'control' cluster could affect the types of participants recruited.

(ii) Cluster-randomised trials often randomise all clusters at once, so lack of concealment of an allocation sequence should not usually be an issue. However, because small numbers of clusters are randomised, there is a possibility of chance baseline imbalance between the randomised groups, in terms of either the clusters or the individuals. Although not a form of bias as such, the risk of baseline differences can be reduced by using stratified or pair-matched randomisation of clusters. Reporting of the baseline comparability of clusters, or statistical adjustment for baseline characteristics, can help reduce concern about the effects of baseline imbalance.

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(iii) Occasionally, complete clusters are lost from a trial, and have to be omitted from the analysis. Just as for missing outcome data in individually randomised trials, this may lead to bias. In addition, missing outcomes for individuals within clusters may also lead to a risk of bias in cluster-randomised trials.

(iv) Many cluster-randomised trials are analysed by incorrect statistical methods, not taking the clustering into account. Such analyses create a 'unit of analysis error' and produce over-precise results (the standard error of the estimated intervention effect is too small) and P values that are too small. They do not lead to biased estimates of effect. However, if they remain uncorrected, they will receive too much weight in a meta-analysis.

(v) In a meta-analysis including both cluster and individually randomised trials, or including cluster-randomised trials with different types of clusters, possible differences between the intervention effects being estimated need to be considered. For example, in a vaccine trial of infectious diseases, a vaccine applied to all individuals in a community would be expected to be more effective than if the vaccine was applied to only half of the people. Another example is provided by a Cochrane Review of hip protectors. The cluster trials showed large positive effect, whereas individually randomised trials did not show any clear benefit. One possibility is that there was a 'herd effect' in the cluster-randomised trials (which were often performed in nursing homes, where compliance with using the protectors may have been enhanced). In general, such 'contamination' would lead to underestimates of effect. Thus, if an intervention effect is still demonstrated despite contamination in those trials that were not cluster-randomised, a confident conclusion about the presence of an effect can be drawn. However, the size of the effect is likely to be underestimated. Contamination and 'herd effects' may be different for different types of cluster.

CONTRIBUTIONS OF AUTHORS

Zhiliang Caleb Lin: conceived, designed, and coordinated the review; extracted data; checked the quality of data extraction; analysed or interpreted data; undertook and checked quality assessment; performed statistical analysis; checked the quality of the statistical analysis; produced the first draft of the review; contributed to writing and editing the review; performed previous work that was the foundation of the current review; wrote to study author/experts/companies; performed translations; and approved the final review prior to publication.

Paula Loveland: extracted data; checked the quality of data extraction; analysed or interpreted data; undertook and checked quality assessment; produced the first draft of the review; contributed to writing or editing the review; and approved the final review prior to publication.

Renea Johnston: designed and coordinated the review; extracted data; checked the quality of data extraction; analysed or interpreted data; undertook and checked quality assessment; performed statistical analysis; checked the quality of the statistical analysis; produced the first draft of the review; contributed to writing or editing the review; advised on the review; performed previous work that was the foundation of the current review; and approved the final review prior to publication.

Michael Bruce: contributed to writing or editing the review and advised on the review.

Carolina Weller: conceived, designed, and coordinated the review; checked the quality of data extraction; analysed or interpreted data; undertook and checked quality assessment; produced the first draft of the review; contributed to writing or editing the review; secured funding; performed previous work that was the foundation of the current review; approved the final review prior to publication; and is a guarantor of the review.

Contributions of the editorial base

Kurinchi Gurusamy (Editor): edited the protocol; advised on methodology, interpretation, and protocol content; approved the final protocol prior to publication.

Jo Dumville (Coordinating Editor): edited the review; advised on methodology, interpretation, and review content; approved the final review prior to publication.

Gill Rizzello (Managing Editor): coordinated the editorial process; advised on content; edited the protocol and review.

Reetu Child, Naomi Shaw and Sophie Bishop (Information Specialists): designed the search strategy; ran the searches; and edited the search methods section.

Ursula Gonthier (Editorial Assistant): edited the Plain language summary and references sections of the protocol and the review.

DECLARATIONS OF INTEREST

Zhiliang Caleb Lin: none known.

Paula Loveland: none known.

Renea Johnston: none known.

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Michael Bruce: none known.

Carolina Weller: none known.

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  In kind support

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

1. The title for the protocol for this review was "Subfascial endoscopic perforator surgery (SEPS) for treating and preventing venous leg ulcers". After consulting with Cochrane Wounds Editors, we have modified this to "Subfascial endoscopic perforator surgery (SEPS) for treating venous leg ulcers". This reflects the inclusion criteria of participants with active venous ulcers better, as to answer the question of recurrence properly, we would have had to also include participants with previous ulcers which had closed.

2. In our protocol CD012164, under 'Types of interventions', our protocol reads: "SEPS performed in conjunction with other surgical interventions are not expected, but if we identify trials of SEPS plus another surgery we will exclude these from this review."

This was an error identified post publication of the protocol and discussed at the time with the Cochrane Wounds editorial base. We have now rectified this, and trials of SEPS plus another surgery have been included in the review as originally intended.

3. With the agreement of the Cochrane Wounds editorial base, we also added an explicit comparator to the following sentence, again under 'Types of interventions'; our protocol reads: "It is expected that all treatment groups will receive compression bandaging (Nelzen 2011). Our presentation and analysis of results will be organised by a common comparator, e.g. SEPS versus sham as the main comparator; followed by SEPS versus conservative management, etc."

We have amended this to: "It was expected that all treatment groups will receive compression bandaging (Nelzen 2011). Our presentation and analysis of results will be organised by a common comparator, e.g. SEPS versus sham as the main comparator; followed by SEPS versus conservative management, SEPS plus superficial venous surgery versus superficial venous surgery alone."

4. We had planned to extract data at 6-, 12-, and 24-month time points, and present only the 24-month data in the 'Summary of findings' table. However, two studies only measured ulcer recurrence rate at other time points, (18 months - Callini 2002), (60 months - Pierik 1997), so rather than exclude these data, we included these time points in our analyses.

INDEX TERMS

Medical Subject Headings (MeSH)

Compression Bandages; Postoperative Complications; Randomized Controlled Trials as Topic; Recurrence; Saphenous Vein [surgery]; Time Factors; Varicose Ulcer [*surgery]; Vascular Surgical Procedures [adverse effects] [methods]; Veins [*surgery]; Wound Healing

MeSH check words

Adult; Aged; Aged, 80 and over; Female; Humans; Male; Middle Aged

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