Endovenous thermal ablation for healing venous ulcers and preventing recurrence (Review)

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[Intervention Review]

Endovenous thermal ablation for healing venous ulcers and preventing recurrence

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ABSTRACT

Background

Venous leg ulcers represent the worst extreme within the spectrum of chronic venous disease. Affecting up to 3% of the adult population, this typically chronic, recurring condition significantly impairs quality of life, and its treatment places a heavy financial burden upon healthcare systems. The current mainstay of treatment for venous leg ulcers is compression therapy, which has been shown to enhance ulcer healing rates. Open surgery on the veins in the leg has been shown to reduce ulcer recurrence rates, but it is an unpopular option and many patients are unsuitable. The efficacy of the newer, minimally-invasive endovenous thermal techniques has been established in uncomplicated superficial venous disease, and these techniques are now beginning to be used in the management of venous ulceration, though the evidence for this treatment is currently unclear. It is hypothesised that, when used with compression, ablation may further reduce pressures in the leg veins, resulting in improved rates of healing. Furthermore, since long-term patient concordance with compression is relatively poor, it may prove more popular, effective and cost-effective to provide a single intervention to reduce recurrence, rather than life-long treatment with compression.

Objectives

To determine the effects of superficial endovenous thermal ablation on the healing, recurrence and quality of life of people with active or healed venous ulcers.

Search methods

In August 2013 we searched Cochrane Wounds Group Specialised Register; The Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*); Ovid MEDLINE; Ovid MEDLINE (In-Process & Other Non-Indexed Citations); Ovid EMBASE; and EBSCO CINAHL. There were no restrictions on the language of publication but there was a date restriction based on the fact that superficial endovenous thermal ablation is a comparatively new medical technology.

Selection criteria

Randomised clinical trials comparing endovenous thermal ablative techniques with compression therapy alone for venous leg ulcers were eligible for inclusion. Trials had to report on at least one objective measure of ulcer healing (primary outcome) such as proportion of ulcers healed at a given time point, time to complete healing, change in ulcer size, proportion of ulcers recurring over a given time period, or at a specific point, and ulcer-free days. Secondary outcomes sought included patient-reported quality of life, economic data and adverse events.

Data collection and analysis

Details of potentially eligible studies were extracted and summarised using a data extraction table. Data extraction and validity assessment were performed independently by two review authors, and any disagreements resolved by consensus or by arbitration of a third review author.

Main results

No eligible randomised controlled trials were identified. There is an absence of evidence regarding the effects of superficial endovenous thermal ablation on ulcer healing, recurrence or quality of life of people with venous leg ulcer disease.

Authors' conclusions

The review identified no randomised controlled trials on the effects on ulcer healing, recurrence or quality of life, of superficial endovenous thermal ablation in people with active or healed venous leg ulcers. Adequately-powered, high quality randomised controlled trials comparing endovenous thermal ablative interventions with compression therapy are urgently required to explore this new treatment strategy. These should measure and report outcomes that include time to ulcer healing, ulcer recurrence, quality of life and cost-effectiveness.

PLAIN LANGUAGE SUMMARY

Endovenous thermal ablation for treating venous leg ulcers

The veins of the leg are designed to return blood from the leg upwards towards the heart. Blood is under the force of gravity and, left to itself, would flow downwards. Valves within the veins normally prevent blood from flowing downwards (i.e. backwards), however, if these valves become leaky, pressure within the veins increases. This high pressure causes swelling, thickening and damage to skin, which may break down to form ulcers. Venous leg ulcers are associated with pain and mobility restrictions that affect quality of life.

Compression of legs with bandages or medical stockings helps to move the blood upwards, and reduces pressure in the veins and tissues. This treatment has been shown to improve ulcer healing. Compression is unpopular because it can be uncomfortable, and only provides a benefit while the bandages or hosiery are worn. Even with compression treatment, healing of venous ulcers may still take a long time, and ulcers often come back.

Traditionally, surgery for venous disease involves removing the veins from the leg. The blood is then diverted through the remaining healthy veins. This reduces the pressure in the veins and helps prevent ulcers that have healed from coming back. Generally, this surgery is performed under a general anaesthetic and involves a period of recovery. Some people, particularly the elderly, are less suitable for general anaesthetic and may be at risk of age-related complications or a prolonged and difficult recovery. Newer 'keyhole' surgical techniques destroy the veins with heat, and require only local anaesthesia. These treatments have been shown to be as effective as surgery in the treatment of varicose veins in the absence of ulcers, and result in less pain than traditional surgery. Since a general anaesthetic can be avoided, there is also a reduced risk associated with the anaesthetic procedure, and the recovery period is shorter.

The purpose of this review was to compare the effectiveness of these new, minimally invasive surgical techniques with compression therapy for the management of venous leg ulcers. We wanted to see how well the different treatments work in terms of ulcer healing and recurrence rates. However, despite extensive searching of the literature, we could find no high quality evidence that could provide any answers to the question, so further evidence is needed in this area before any conclusions can be drawn.

BACKGROUND

Venous ulcer disease is thought to have an overall prevalence of approximately 1% to 3% in the adult population (Fletcher 2003; Gallenkemper 2008; Graham 2003; Grey 2006), which increases with age and is more common in women (Baker 1991; Callam 1985; Iglesias 2004; Lees 1992; London 2000; Margolis 2002). Prevalence of active ulceration is quoted at up to 0.5%, while healed ulcers affect up to 2.4% of people over the age of 70 (

Gallenkemper 2008; Gloviczki 2009). Overall incidence rates are in the region of 15 to 30 per 100,000 person years in the western world (Gallenkemper 2008; Heit 2001).

Active ulceration is known to have a profoundly detrimental effect upon quality of life, including significant pain and restriction in mobility, which result in limitations of physical and social roles (Carradice 2011a; Hareendran 2005; Herber 2007; Iglesias 2005; Michaels 2009). Healing times are often protracted, sometimes taking many years, with some ulcers failing to heal (Moffatt 1995; Ruckley 1998). One large trial found that even with treatment and close monitoring, only 65% of ulcers healed within 24 weeks and only around 90% within three years (Barwell 2004). Once healed, venous ulcers are subject to cyclical recurrence, with recurrence rates of between 26% to 70% occurring within the year after healing (Barwell 2004; Franks 1995; Ghauri 2000; Grey 2006; Lees 1992; Monk 1982).

Description of the condition

The aetiology (cause) of venous ulceration is poorly understood. The underlying issue is one of relative venous hypertension (increased pressure in the veins) (see Appendix 1). Normally the veins in the calf are compressed during muscle contraction (walking), causing a flow of blood, against gravity,towards the heart. Valves in the veins prevent retrograde (reverse) flow back into the leg. Occlusion of these veins, or more commonly, incompetence of the valves (see Appendix 1), interferes with this physiology, and pressure within the veins of the leg increases. This back-pressure on the capillaries within the soft tissues causes inflammation and interruption of gaseous exchange between cells and the capillaries. These effects culminate in skin breakdown and ulcer formation after minor, innocuous trauma, or even spontaneously. Furthermore, healing is prolonged, or even arrested, due to the hostile environment created by these processes.

There are two systems of veins in the leg: the deep system and the superficial system; these communicate with each other at two main junctions, the saphenofemoral junction in the groin, and the saphenopopliteal junction behind the knee. Valvular incompetence that causes venous reflux is the most frequent underlying mechanism for chronic venous hypertension. Among patients with ulcers, 51% to 53% have isolated reflux in the superficial system, 32% to 44% have reflux in both the deep and superficial systems, and in 5% to 15% of patients reflux is confined to the deep system alone (Barwell 2004).

A number of incompetent 'perforating' veins between the superficial and deep systems may also be present, though they are highly variable and a systematic review of current evidence failed to confirm optimal timing or treatment technique for incompetent perforators (Gloviczki 2011). Discussion of the role of perforators is beyond the scope of this review. Venous ulcer disease describes the most severe end of a spectrum of chronic venous insufficiency, as categorised by the CEAP (Clinical severity, Anatomy, Etiology and Pathophysiology) classification system. Clinical severity is scored from C0 (no disease) to C6 (active ulceration); C5 describes a healed ulcer (Eklof 2004).

Description of the intervention

Existing treatment

The current mainstay of treatment for venous ulcers is compression therapy. This treatment has clearly been shown to improve ulcer healing rates (O'Meara 2009; Partsch 2008), and is thought to work by increasing interstitial pressure in the tissues and facilitating increased venous return, hence reducing venous hypertension in the limb. There are many different variations of compression systems, but multi-component systems (including several layers of different materials) appear to be more effective than single-component systems (O'Meara 2009). Significant costs are associated with the treatment of venous ulceration because of the chronic and relapsing nature of the condition, and the need for high levels of nursing, and, in some cases, social care. Western healthcare systems spend around 1% to 3% of their budget in this area (Bosanquet 1992; Ellison 2002; Gallenkemper 2008; Gloviczki 2009; Kurz 1999; Nelzen 2000; Purwins 2010; Ragnarson 2005; Ruckley 1997; Van den Oever 1998), and in the USA alone, treatment of venous ulcers costs around USD 3 billion per year (McGuckin 2002). Compression treatment only offers a benefit during active treatment and it can be bulky and uncomfortable to wear which affects compliance. The impact on the quality of life of patients and their relatives, alongside the significant costs of treatment, ensure that the stakes are high for improving the outcomes for this group of patients.

A randomised controlled trial from the UK has shown that conventional superficial venous ligation and stripping, in addition to compression bandaging, significantly reduced the recurrence of venous ulceration after healing, although the overall time to achieve healing was unaffected (Barwell 2004). However it has been suggested that the lack of a measurable effect on healing may have been due to a lack of statistical power in this study (in which participants with healed rather than open ulcers predominated).

Furthermore people with venous ulcer disease are typically elderly, and many have significant co-morbidities. Consequently, a significant proportion are judged to be unsuitable for conventional surgery under a general anaesthetic. Previous work also suggests that around 25% of patients refuse conventional surgery when it is offered (Ghauri 1998). These factors have limited the impact of surgery in the management of venous ulcer disease.

Endovenous thermal ablation

Endovenous thermal ablative techniques have increased in popularity since 1998 (Carradice 2008; HES online 2012). These minimally invasive procedures involve the application of duplex-guided, catheter-directed thermal energy inside the incompetent superficial veins themselves, to result in a permanent vein occlusion (blockage) (see Appendix 1). The blood will then return from the leg via the remaining healthy superficial and deep veins.

Method of thermal energy delivery

Thermal energy causes collagen to contract and endothelium to be denuded; occlusion of the vein is caused by thickening of the vein wall, contraction of the lumen and fibrosis of the vein.There are two broad mechanisms of thermal energy delivery. The first technique is called Endovenous Laser Treatment or Endovenous Laser Ablation (EVLT/EVLA). This involves transmission of laser energy down an optical fibre placed within the vein. This energy is absorbed by haemoglobin (see Appendix 1), or water, present inside the vessel and its wall, creating heat.

The second mechanism is Radiofrequency Ablation (RFA), in which a catheter-mounted electrode is introduced into the vein. An electrical current is passed through either a metal coil at the tip of the catheter, or through the vein wall itself via two electrodes. The electrical current, therefore, applies heat directly, or indirectly, through the vein wall.

All of these endovenous thermal ablation interventions can be readily undertaken under local anaesthetic in a clean procedure room. To date, they have been used primarily to treat symptomatic varicose veins, but interest is growing in their use in the context of venous ulceration

How the intervention might work

As venous hypertension is thought to be the underlying cause of venous ulceration, it is hoped that surgical intervention aimed at resolving the hypertension itself will result in healing and a reduction in ulcer recurrence. The four-year follow-up of the ESCHAR study highlighted the value of removal of superficial venous incompetence (by the surgical removal of the veins themselves) in addition to compression therapy (Gohel 2007). Endovenous thermal ablation of the incompetent superficial venous system may demonstrate similar benefits, but with potential advantages over conventional surgery.

The 'walk-in, walk-out' local anaesthetic technique that can be used with endovenous thermal ablation may be more acceptable to patients with venous ulcers, avoiding the difficulties associated with general anaesthesia and minimising the morbidity, recovery time and even early recurrence following intervention (Carradice 2011b; Carradice 2011c; Darwood 2008; Disselhoff 2008; Mekako 2006; Subramonia 2010). As these techniques can be performed in an 'office-based' environment rather than traditional surgical facilities, it may be feasible to use them in less wealthy regions and economies.

Why it is important to do this review

Venous ulceration is a particularly challenging problem that results in significant impairment of quality of life, and its treatment places a heavy financial burden on healthcare systems. Relatively new endovenous techniques are popular in uncomplicated venous disease and, anecdotally, their use is growing in the management of venous ulcers. A systematic review and appraisal of the existing evidence for the effects of endovenous ablation on venous ulcer healing and recurrence will assess whether evidence based recommendations can be made to guide decisions regarding future implementation of the technique and the needs for further research.

OBJECTIVES

To determine the effects of superficial endovenous thermal ablation upon the healing, recurrence and quality of life of people with active or healed venous ulcers.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised clinical trials (RCTs) comparing endovenous thermal ablative techniques with conservative management, which may include compression therapy.

Types of participants

Studies recruiting participants of any age undergoing treatment for venous ulcer disease (levels C5 (healed venous ulcer) and C6 (active venous ulcer)) in which venous reflux was demonstrated in the superficial venous system pre-operatively using duplex ultrasound. We planned to exclude studies where ulceration was thought to be of a mixed or non-venous aetiology (e.g. arterial, vasculitis), as well as those involving participants with an ankle brachial pressure index (ABPI) of less than 0.8 or who required interventions for peripheral arterial disease.

Types of interventions

Studies comparing (an) endovenous thermal ablative technique(s) with conservative management. We planned to include any endovenous thermal ablative technique including endovenous laser and endovenous radiofrequency ablation in all its applications. Trials were also eligible for inclusion if compression therapy was given in addition to treatment as long as it was given to all trial participants irrespective of group allocation.

Types of outcome measures

To be eligible for inclusion, trials had to report at least one of the primary outcomes (below). We stipulated this since most the majority of studies of endovenous ablation are aimed at treating venous reflux rather than venous ulcers:

Primary outcomes

Objective measures of healing such as the following:

- proportion of ulcers healed at a given time point;
- time to complete healing;
- change in ulcer size (measured objectively);
- proportion of ulcers recurring over a given time period, or time to recurrence;
- ulcer-free days over a given time period.

Secondary outcomes

Secondary outcomes include:

- quality of life (patient-reported);
- economic data;
- adverse events.

Search methods for identification of studies

Electronic searches

In August 2013 we searched the following electronic databases to find reports of relevant RCTs:

- Cochrane Wounds Group Specialised Register (searched 28 August, 2013);
- The Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2013, Issue 7);
- Ovid MEDLINE (1998 to August Week 2 2013);
- Ovid MEDLINE (In-Process & Other Non-Indexed Citations August 27, 2013);
- Ovid EMBASE (1998 to 2013 Week 34);
- EBSCO CINAHL (1982 to 23 August 2013)

We used the following search strategy in the Cochrane Central Register of Controlled Trials (CENTRAL):

#1 MeSH descriptor Laser Therapy explode all trees
#2 "endovenous laser" or EVL or EVLA or EVLO or EVLT: ti,ab,kw
#3 MeSH descriptor Catheter Ablation explode all trees
#4 "radiofrequency ablation" or RFA or RFO:ti,ab,kw
#5 VNUS or ClosureFAST or Closure:ti,ab,kw
#6 VCF or "bipolar radiofrequency induced thermotherapy" or RFITT:ti,ab,kw
#7 (#1 OR #2 OR #3 OR #4 OR #5 OR #6)
#8 MeSH descriptor Leg Ulcer explode all trees
#9 (varicose NEXT ulcer*) or (venous NEXT ulcer*) or (leg NEXT ulcer*) or (stasis NEXT ulcer*) or ((lower NEXTextremit*) NEAR/2 ulcer*) or (crural NEXT ulcer*) or ulcus cruris:ti,ab,kw
#10 MeSH descriptor Venous Insufficiency explode all trees
#11 "chronic venous insufficiency" or CVI:ti,ab,kw
#12 (#8 OR #9 OR #10 OR #11)
#13 (#7 AND #12)

The search strategies for Ovid MEDLINE, Ovid EMBASE and EBSCO CINAHL can be found in Appendix 2. The Ovid MEDLINE search was then combined with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximising version (2008 revision) (Lefebvre 2011). The EMBASE and CINAHL searches were combined with the trial filters developed by the Scottish Intercollegiate Guidelines Network (SIGN 2011). There was no restriction on the language of publication, but there was a date restriction based on the fact that superficial endovenous thermal ablation is a comparatively new medical technology.

The following trial registries were also searched:

- the Australian New Zealand Clinical Trials Registry: http://www.anzctr.org.au/;
- ClinicalTrials.gov register: http://www.clinicaltrials.gov/;
- the WHO International Clinical Trials Registry Platform Search Portal: http://www.who.int/trialsearch; and
- the Current Controlled Trials meta-search engine: http://www.controlled-trials.com/

Searching other resources

The bibliographies of trials identified by the above strategies were searched for further studies. Relevant companies were contacted to see if they had any unpublished data that could contribute towards this review (Including Angiodynamics, Covidien and Biolitec).

Data collection and analysis

Review authors were not blinded in the selection of studies, the assessment of bias or the extraction of data.

Selection of studies

Two review authors (NS, TW) independently assessed the titles and available abstracts of all studies identified by the initial search and excluded any clearly irrelevant studies. Full paper copies of reports of potentially eligible studies were assessed independently against the inclusion criteria. Disagreements about inclusion were resolved by consensus, and, if this failed, by the arbitration of a third review author (DC).

Data extraction and management

Two review authors (NS, TW) independently extracted data, including information on source of funding, study population, interventions, analyses and outcomes, using a standardised data extraction form. Study authors were contacted to obtain further information; where required.

We planned to extract raw data for outcomes of interest (means and standard deviations for continuous outcomes, number of events for dichotomous outcomes, and hazard ratio and 95% confidence intervals for time-to-event data) from the published reports. We had planned to record whether the data were converted, or imputed, in the notes section of the 'Characteristics of included studies' table.

Assessment of risk of bias in included studies

We planned to assess risk of bias of the included studies independently against key criteria, including: random sequence generation; allocation concealment; blinding of participants, personnel and outcomes; incomplete outcome data; selective outcome reporting; and other sources of bias (such as whether groups were similar at baseline for important prognostic indicators - infection, wound size and severity, duration of ulcers; and if co-interventions were avoided or were similar between the treatment and control groups) in accordance with the methods recommended by The Cochrane Collaboration (Higgins 2011a). Each of these criteria were to be explicitly judged using the following categories: 'low risk of bias', 'high risk of bias' or 'unclear' (due either to a lack of information or uncertainty over the potential for bias).

Measures of treatment effect

We planned to chart the results of each included study on forest plots as point estimates, i.e. risk ratios (RR) with corresponding 95% confidence intervals (CI) for dichotomous outcomes, mean difference (MD) with 95% CI for continuous outcomes, and hazard ratio (HR) with 95% CI for time-to-event outcomes (e.g. time to healing). If the results could not be shown in this way, we planned to report them in the text of the review. For continuous measures, we had planned to calculate mean differences, if possible, as these results are easier for clinicians/readers to interpret. If individual outcome measures had varied, but the construct being measured had been the same (i.e. use of different scales across trials or inability to convert data into the same scale, or both), then we had planned to use standardised mean differences (SMD).

Unit of analysis issues

RCTs that randomise or allocate clusters, but do not account for clustering during analysis (and thus may have potential unit of analysis errors), were to be re-analysed by calculating effective sample sizes where possible, according to the recommended Cochrane methods (Higgins 2011b). We had planned to incorporate an estimate of the intra-cluster coefficient (ICC) using external estimates obtained from similar studies, if necessary.

Dealing with missing data

Where data or information were missing from the trial reports; we had planned to contact the trial authors were to provide this. Where it was not possible to ascertain the healed status of patients, we planned to report data based on two assumptions: 1) healing followed by no recurrence, and 2) non-healing followed by recurrence, and to perform a sensitivity analysis on the effect of these extreme assumptions.

Assessment of heterogeneity

Prior to meta-analysis, we had planned to assess studies for clinical homogeneity with respect to patient demographics, types of therapy, comparator treatment and the nature of the outcomes reported. We did not intend to combine clinically heterogeneous studies in the analysis, but to describe them separately. For studies judged as clinically homogeneous, we planned to test statistical heterogeneity with the Q test (Chi^2 and the I^2 statistic). We would have interpreted a Chi^2 test resulting in a P value less than 0.10 as indicating significant statistical heterogeneity. In order to assess and quantify the possible magnitude of heterogeneity across studies, we planned to use the I^2 statistic - a rough guide to its interpretation follows:

- 0% to 40% would be viewed as indicative of low levels of heterogeneity that may not be important;
- 30% to 60% may represent moderate heterogeneity;
- 50% to 90% would represent substantial heterogeneity;
- 75% to 100% would represent considerable heterogeneity and unsuitability for meta-analysis (Deeks 2011).

Assessment of reporting biases

As with conduct bias, two review authors independently assessed any evidence of reporting bias and reported this as recommended (Higgins 2011a). Where there was doubt, the study authors were contacted for clarification, to acquire unpublished data and provide an English language version of the original trial protocol in order to assess the risk of bias.

Data synthesis

For clinically homogeneous studies with similar participants, comparators and the same outcome measures, we aimed to pool outcomes in a meta-analysis. We planned to use a fixed-effect model for meta-analysis, but in the presence of heterogeneity that might be important (I^2 statistic of 40% or more) we planned to use a random-effects model. For time-to-event data, we planned to convert estimates of hazard ratio (HR) and 95% CI, if presented in the trial reports, into the log rank observed minus expected events and variance of the log rank, and pool these estimates using a fixed-effect model (Deeks 2011).

Subgroup analysis and investigation of heterogeneity

We planned to perform subgroup analyses to determine whether effect size was influenced by the following factors:

- severity of ulcers at baseline, determined by size (more than 5 cm^2 versus 5 cm^2 or less) or ulcer duration (more than six months versus six months or less) at baseline;
- different endovenous thermal techniques;
- different forms of compression;
- the presence of infection (determined by clinical features and positive culture); and
- aetiology of the ulcer (occlusive or reflux).

Sensitivity analysis

We hoped to conduct a sensitivity analysis to investigate the robustness of the treatment effect to allocation concealment, by removing trials that did not report adequate allocation concealment from the meta-analysis to see if this changed the overall treatment effect. We also planned to do this for blinded outcome assessment.

RESULTS

Description of studies

See: Characteristics of excluded studies

Results of the search

Electronic searches produced 242 references, 238 of which could be excluded on the basis of their titles and abstracts. This left four studies that were retrieved in full for consideration for inclusion in this review.

Included studies

After detailed review of manuscripts and protocols, and discussion with the study authors, it was decided that no studies fulfilled the inclusion criteria.

Excluded studies

All four studies screened failed to meet the eligibility criteria (See Characteristics of excluded studies). Three were excluded because they were case series and provided no comparative data (Pannier 2007; Sharif 2007; Teo 2010). The fourth study was presented as a randomised clinical trial that compared combined EVLA plus compression therapy with compression therapy alone in people with active venous ulcers (Viarengo 2007). However, following detailed examination and correspondence with the authors, this study was excluded because the first participant had been randomised by the selection of a coloured card, with all other participants allocated to treatment group alternately thereafter. This study was, therefore, a quasi-randomised trial.

Risk of bias in included studies

Risk of bias could not be assessed because no studies were included in this review.

Allocation

Allocation, with respect to selection bias, could not be assessed because no studies were included in this review.

Blinding

Blinding could not be assessed because no studies were included in this review.

Incomplete outcome data

Attrition bias could not be assessed because no studies were included in this review.

Selective reporting

Reporting bias could not be assessed because no studies were included in this review.

Other potential sources of bias

Other potential sources of bias could not be assessed because no studies were included in this review.

Effects of interventions

Effects of interventions could not be determined because no studies were included in this review.

Agreements and disagreements with other studies or reviews

There are no other studies or reviews on this issue to date of which we are aware. A separate review will look at the effects of endovenous chemical ablation.

DISCUSSION

Summary of main results

No eligible randomised clinical trials were identified that compared endovenous thermal ablation with conservative treatment for healing venous ulcers or preventing recurrence. This clearly demonstrates the current deficiency of Level 1 evidence in this new area of study. Only one comparative study was identified (Viarengo 2007), but this was excluded because it was a quasi-randomised trial and judged to be at high risk of selection bias.

In this trial, 52 consecutive patients with active ulcers, that were thought to be due to demonstrable superficial venous insufficiency and present for more than a year, were allocated to receive one of two treatment strategies: Group 1 (n = 25) received conservative treatment consisting of "elastic or inelastic compression therapy", while Group 2 (n = 27) received EVLA of the great or small saphenous vein followed by "elastic or inelastic compression therapy". The authors were vague about the quality of care, types of compression used, and the management of ulcers following healing, and similarly, the details of the EVLA procedures were poorly reported. Whilst the proportion of people with healed ulcers was significantly higher in the group that received endovenous thermal ablation at three months (63% versus 12%), six months (82% versus 20%) and 12 months (82% versus 24%) (P value 0.001), the study was at high risk of selection bias and poorly reported.

In conclusion, there is an absence of evidence regarding the effects on venous ulcer healing, recurrence or associated quality of life, of endovenous thermal ablation. Adequately powered, high quality randomised controlled trials are urgently needed of this potentially promising treatment.

Potential biases in the review process

The reviewers have previously performed research on endovenous thermal ablation in patients with uncomplicated, superficial venous insufficiency without ulceration. The reviewers were not blinded regarding the source of the studies under evaluation.

AUTHORS' CONCLUSIONS

Implications for practice

There are no randomised controlled trials of endovenous thermal ablation as a treatment for venous leg ulcers. High quality RCTs are required before this treatment becomes implemented into practice.

Implications for research

Despite the fact that minimally invasive endovenous thermal interventions have been used in clinical practice for over a decade, there are no RCTs evaluating its effects on venous ulcer disease and only one quasi-randomised study. High quality RCTs are urgently needed.

Future studies need to be designed and reported with the Consolidated Standards of Reporting Trials (CONSORT) statement in mind (CONSORT 2010). Future studies should be randomised controlled trials, in which multicentred results can be generalised with greater confidence. Blinding in such studies is always very difficult, as sham surgery would clearly be unethical, but with adequate resources it is possible to blind aspects of the assessment and analysis. A sample size calculation based upon the primary outcome measure should be performed, and outcomes should be defined clearly and be as objective as possible. Outcomes should include ulcer healing rates, ulcer recurrence rates, adverse events, quality of life and the cost of treatment, and should be measured equitably in both groups. The conservative management group should receive high-quality care including compression treatment, and compliance with dressings should be recorded.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Study	Reason for exclusion
Pannier 2007	Case series
Sharif 2007	Case series
Teo 2010	Case series
Viarengo 2007	Quasi-randomisation: allocation of treatment without clear description of sequence generation in the publication. However personal communication from the authors stated that the first case was decided by a draw held by the patient through red and blue cards, in which the red card allocated compression therapy and the blue card combined compression and EVLA treatment. From this initial treatment chosen by draw, subsequent patients were allocated alternately to compression or compression plus EVLA treatment

Abbreviation
EVLA = endovenous laser ablation

DATA AND ANALYSES

This review has no analyses.

APPENDICES

Appendix 1. Glossary of terms

Catheter: a tube that delivers something into or out of the body.
Cytotoxic: poisonous to the body's cells.
Duplex ultrasound: technology that involves the reflection of ultrasound waves fired into the body to create a real-time picture of the veins inside the body, and to show the speed and direction of blood flow within them.
Extravasation: part of the inflammatory process during which the cells and chemicals involved in inflammation (inflammatory exudates) move from a blood vessel into the surrounding tissues.
Inflammatory process/inflammation: the body's natural response to tissue damage that can be dysfunctional and leave lasting tissue damage.
Haemoglobin: the iron-containing red pigment in red blood cells, responsible for carrying oxygen to the body's cells.
Oedema: the process whereby fluid leaves the bloodstream and moves into tissue, causing swelling.
Post-thrombotic syndrome: deep venous thrombosis results in reflux, occlusion or changes in vessel wall compliance and stiffness. This tends to result in advanced tissue damage, swelling and ulceration due to the development of significant venous hypertension.
Venous hypertension: high blood pressure within the veins.
Venous incompetence/insufficiency/reflux: the presence of abnormal retrograde (reverse) flow within the veins caused by valvular dysfunction.

Appendix 2. Search strategies for Ovid MEDLINE, Ovid EMBASE and EBSCO CINAHL

Ovid Medline

1 exp Laser Therapy/ (29930)
2 (endovenous laser or EVL or EVLA or EVLO or EVLT).tw. (627)
3 exp Catheter Ablation/ (18344)
4 (radiofrequency ablation or RFA or RFO).tw. (7544)
5 (VNUS or ClosureFAST).tw. (42)
6 (VNUS or ClosureFAST or VCF or bipolar radiofrequency induced thermotherapy or RFITT).tw. (318)
7 or/1-6 (50041)
8 exp Leg Ulcer/ (10174)
9 (varicose ulcer* or venous ulcer* or leg ulcer* or stasis ulcer* or crural ulcer* or ulcus cruris).tw. (3714)
10 exp Venous Insufficiency/ (3000)
11 (chronic venous insufficiency or CVI).tw. (1783)
12 or/8-11 (14022)
13 7 and 12 (359)
14 randomized controlled trial.pt. (253655)
15 controlled clinical trial.pt. (40653)
16 randomized.ab. (207525)
17 placebo.ab. (95368)
18 clinical trials as topic.sh. (82163)
19 randomly.ab. (142445)
20 trial.ti. (77704)

21 or/14-20 (571938)
22 (animals not (humans and animals)).sh. (1681151)
23 21 not 22 (519938)
24 13 and 23 (60)

Ovid Embase

1 exp low level laser therapy/ (11046)
2 (endovenous laser or EVL or EVLA or EVLO or EVLT).tw. (1202)
3 exp catheter ablation/ (19506)
4 (radiofrequency ablation or RFA or RFO).tw. (13098)
5 (VNUS or ClosureFAST).tw. (89)
6 (VNUS or ClosureFAST or VCF or bipolar radiofrequency induced thermotherapy or RFITT).tw. (576)
7 or/1-6 (40835)
8 exp leg ulcer/ (6337)
9 (varicose ulcer* or venous ulcer* or leg ulcer* or stasis ulcer* or crural ulcer* or ulcus cruris).tw. (5733)
10 exp vein insufficiency/ (5251)
11 (chronic venous insufficiency or CVI).tw. (2932)
12 or/8-11 (13626)
13 7 and 12 (436)
14 Clinical trial/ (726183)
15 Randomized controlled trials/ (37624)
16 Random Allocation/ (53146)
17 Single-Blind Method/ (16705)
18 Double-Blind Method/ (90046)
19 Cross-Over Studies/ (33876)
20 Placebos/ (176715)
21 Randomi?ed controlled trial$.tw. (89846)
22 RCT.tw. (12050)
23 Random allocation.tw. (990)
24 Randomly allocated.tw. (15464)
25 Allocated randomly.tw. (1266)
26 (allocated adj2 random).tw. (280)
27 Single blind$.tw. (10463)
28 Double blind$.tw. (95928)
29 ((treble or triple) adj blind$).tw. (260)
30 Placebo$.tw. (146575)
31 Prospective Studies/ (222655)
32 or/14-31 (1123002)
33 Case study/ (18314)
34 Case report.tw. (179315)
35 Abstract report/ or letter/ (536136)
36 or/33-35 (729147)
37 32 not 36 (1092972)
38 animal/ (790907)
39 human/ (9290212)
40 38 not 39 (527354)
41 37 not 40 (1069248)
42 13 and 41 (110)

EBSCO CINAHL

S13 S7 and S12

S12 S8 or S9 or S10 or S11
S11 TI (chronic venous insufficiency or CVI) or AB (chronic venous insufficiency or CVI)
S10 (MH "Venous Insufficiency")
S9 TI (varicose ulcer* or venous ulcer* or leg ulcer* or stasis ulcer* or crural ulcer* or ulcer cruris) or AB (varicose ulcer* or venous ulcer* or leg ulcer* or stasis ulcer* or crural ulcer* or ulcer cruris)
S8 (MH "Leg Ulcer+")
S7 S1 or S2 or S3 or S4 or S5 or S6
S6 TI (VNUS or ClosureFAST or VCF or bipolar radiofrequency induced thermotherapy or RFITT) or AB (VNUS or ClosureFAST or VCF or bipolar radiofrequency induced thermotherapy or RFITT)
S5 TI (VNUS or ClosureFAST) or AB (VNUS or ClosureFAST)
S4 TI (radiofrequency ablation or RFA or RFO) or AB (radiofrequency ablation or RFA or RFO)
S3 (MH "Catheter Ablation")
S2 TI (endovenous laser or EVL or EVLA or EVLO or EVLT) or AB (endovenous laser or EVL or EVLA or EVLO or EVLT)
S1 (MH "Laser Therapy+")

Appendix 3. Risk of bias criteria

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 a 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: using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes used without appropriate safeguards (e.g. if envelopes were unsealed or nonopaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.

Unclear

Insufficient information available to permit a 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 to be made, 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 was 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 was likely to introduce bias.

Unclear

Either of the following.

- Insufficient information available to permit a 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 was enough to induce clinically relevant bias in intervention effect estimate.

- For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes was enough to induce clinically relevant bias in observed effect size.
- 'As-treated' analysis done with substantial departure in the intervention received from that assigned at randomisation.
- Potentially inappropriate application of simple imputation.

Unclear

Either of the following.

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

High risk of bias

Any one of the following.

- Not all of the study's pre-specified primary outcomes have been reported.
- One or more primary outcomes were reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified.
- One or more reported primary outcomes were not pre-specified (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 available 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
- stopped early due to some data-dependent process (including a formal-stopping rule); or
- had extreme baseline imbalance; 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.

CONTRIBUTIONS OF AUTHORS

Daniel Carradice: conceived the review question, instigated and reviewed the protocol, co-ordinated the review process, reviewed discussed paper, data and bias, edited and approved the final draft of the report and acts as guarantor of the work.

Nehemiah Samuel: contributed to protocol development, reviewed the papers for inclusion, data and bias, completed the first draft of the report and approved the final version.

Tom Wallace: contributed to protocol development, reviewed the papers for inclusion, data and bias, and approved the final version of the report.

George Smith: contributed to protocol development, edited and approved the final draft of the report.

Ian Chetter: conceived the review concept, contributed to protocol development, edited the report and approved the final draft. Oversight of clinical and intellectual content.

Contributions of editorial base

Nicky Cullum: edited the protocol; advised on methodology, interpretation and protocol content. Approved the final protocol and the review prior to submission.
Sally Bell-Syer: co-ordinated the editorial process. Advised on methodology, interpretation and content. Edited the protocol and the review.
Ruth Foxlee: designed the search strategy and edited the search methods section.

DECLARATIONS OF INTEREST

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Internal sources

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INDEX TERMS

Medical Subject Headings (MeSH)

Catheter Ablation [*methods]; Laser Therapy [*methods]; Recurrence [prevention & control]; Stockings, Compression; Varicose Ulcer [prevention & control; *therapy]; Wound Healing

MeSH check words

Humans