

PROTOCOL

Optimal treatment strategy for mixed arteriovenous leg ulceration: a systematic review protocol

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Plain English Summary

Why we are undertaking this work: A leg wound which fails to heal within two weeks is called an ulcer. Leg ulcers are a serious health problem which happen to one out of every 67 adults and one in every 20 people over the age of 60. This has a large impact upon quality of life and costs the NHS in England more than £3.1 billion every year. In most people with this condition the underlying cause is a disease in the veins in the leg but, in a quarter of cases, there is also disease affecting the arteries. In this case it is called a 'mixed arteriovenous leg ulcer'. There are a range of treatments available for both the arteries and veins and, in some cases, we do not know which treatments to use and in what order so that wounds heal and stop coming back.

What we will do: We will find the studies that looked at different ways of treating people with this condition and combine the results to produce the strategy that best supports healing while being safe.

What this means: Gathering and combining research findings allows us to paint a clearer picture about the best evidence to treat people with this complex and not very well-researched condition. Specifically, in mixed arteriovenous leg ulcers, we will be able to identify if there is a combination of treatments that speeds up healing or is more likely to prevent ulcers from coming back after healing. If strong enough, this information can be used to pave the way for future research that will lead to better care for this group of patients.

Abstract

Introduction: Chronic leg ulceration is a major health problem affecting 1.5% of adults, increasing to 5% of those over 60 years old. It is associated with significant quality of life (QoL) impairment in addition to high treatment costs, estimated at £3.1 billion annually in England alone. In the majority of patients chronic venous disease is the underlying cause, but in a quarter of patients there is also disease affecting the arteries. This situation is often termed mixed arteriovenous leg ulceration (AVLU). Several treatments may be of benefit including arterial intervention, venous intervention, compression therapy, alone and in combination. It is at present uncertain which is the optimal treatment strategy to offer to patients with this condition. The aim of this review is to identify and analyse the available literature evidence and identify the most effective treatment strategy.

Methods: A systematic review will be conducted on the available literature of treatment strategies used for the management of AVLU in line with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines. A search of online databases including OVID Medline and EMBASE will be carried out for comparative prospective studies of patients undergoing treatment of AVLU. The treatment regimens used will be described in full including the sequence and timing of intervention. The primary outcome will be ulcer healing. Secondary outcomes include ulcer recurrence, generic and disease-specific QoL measures, complications and cost-effectiveness. The Covidence software for systematic reviews will be used to screen and select studies. Study data will be extracted onto a Microsoft Excel[®] spreadsheet and summarised in tables. Risk of bias will be assessed using the Cochrane Risk of Bias Tool for randomised trials or the modified Downs and Black checklist for non-randomised studies. Meta-analysis will be performed for homogenous data. Data deemed unsuitable for meta-analysis will be summarised in a narrative fashion.

Conclusion: The findings from this review aim to summarise the current literature in the management of AVLU, including different approaches such as treating venous disease alone or combining treatments to optimise wound healing. This will in turn inform further prospective studies on the optimal treatment strategy for this complex condition.

Key words: arteriovenous ulcers, systematic review protocol

Introduction

Chronic leg ulceration is an increasingly common condition affecting 1.5% of all adults and 3–5% over the age of 60. It is a major challenge to healthcare systems due to the high cost of managing patients with this condition.¹ The National Health Service (NHS) in England treats an estimated 700,000 leg ulcers annually, costing £3.1 billion.^{2–5} This considerable sum is more than double the combined yearly cost of treating colorectal, lung, breast and prostate cancers,⁶ and is additional to the debilitating effect of this condition on patients due to morbidity from pain, immobility and infections.^{7–9} Moreover, the disease and its treatment lead to social isolation and restrictions on daily living such as bathing, clothing choice and walking,^{7–10} all of which have a significant detrimental effect on quality of life (QoL).^{9–11} Indeed, QoL limitation of the physical function of patients with leg ulceration is reported to be similar to those with congestive heart failure.¹¹ The management of chronic leg wounds has been highlighted in the NHS's Long Term Plan as an important area for improvement.⁵ Similarly, this area has been identified as a priority area for research by the James Lind Alliance Priority Setting Partnership in conjunction with the Vascular Research Group.^{12,13}

Mixed arteriovenous ulceration (AVLU) accounts for up to 25% of leg ulcers.^{14–16} This is characterised by a leg wound which fails to heal within two weeks¹⁷ in the presence of both chronic venous disease and peripheral arterial disease.^{14,16,18} A recent National Wound Care Strategy Programme (NWCSP) report identified wide variation in the quality of care received by patients with leg ulcers and that many do not receive effective evidence-based care.⁵ The NWCSP report also highlights that this is a prime area for quality improvement to deliver better patient outcomes and secure better value from resources.⁵ This is perhaps most true of AVLU, where a combination of venous, arterial and wound care-based treatments may be used and there is little consensus on which should be used, and in what order, to provide the best patient outcomes. This contrasts with the evidence for the management of isolated arterial or venous leg ulcers which are well-researched areas with strong evidence to guide treatment.^{18,19}

The optimal management strategy for patients with AVLU remains uncertain. Compression therapy, venous and arterial interventions may all be of benefit, but it is unclear which combinations or sequences lead to optimal wound healing and recurrence prevention. Many clinicians only offer compression therapy after arterial intervention is carried out due to a perception that compression may worsen ischaemia; however, there is good

evidence that compression is safe in the presence of a low ankle brachial pressure index.^{20,21} Moreover, arterial intervention is associated with a significant risk of harm including 1–2% mortality and morbidity in the form of heart attacks, strokes and limb loss.²² Additionally, arterial interventions cost significantly more than office-based venous interventions, which are associated with a much lower risk of harm. An inclusive review of available evidence is therefore needed to guide clinicians towards strategies that optimise benefit and reduce harm to patients. The aim of this review is to identify and analyse the current evidence on the optimal treatment strategy, order and timing of interventions for AVLU.

Methods

A systematic review of the literature will be performed in line with the Cochrane recommendation on conducting reviews of interventions.²³ This protocol was written in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) guidance.²⁴ The main study aim is to identify and synthesise the evidence on different treatment strategies for patients with AVLU. The study protocol has been registered on the International Prospective Register of Systematic Reviews (PROSPERO) database (CRD42024489366).

The study aims to identify the safety, efficacy, effectiveness and cost-effectiveness of treatments for AVLU including compression and intervention for venous and/or arterial disease, alone or in combination. AVLU is defined as the presence of a full-thickness skin defect in the gaiter region with the presence of both clinical class 6 venous disease and an ankle brachial pressure index of <0.9.²⁵

Study eligibility criteria

Original English language articles of prospective comparative studies investigating the effect of compression, arterial intervention, venous intervention or any combination thereof in the treatment of adult patients with AVLU are eligible for inclusion. Conference abstracts, book chapters and retrospective studies will be excluded. Studies that include both patients with critical limb-threatening ischaemia and those with AVLU or those that combine venous leg ulcer patients with AVLU patients will also be excluded, unless the data of patients with AVLU can be analysed separately.

All compression methods including hosiery, bandages, boots or intermittent pneumatic devices are eligible for inclusion. Only arterial interventions recommended for the treatment of peripheral arterial disease by international bodies such as the European

Society for Vascular Surgery (ESVS) will be eligible for inclusion.¹⁹ Similarly, only venous interventions recommended by international bodies such as the ESVS for the treatment of venous reflux or obstruction will be considered eligible.¹⁸

Outcomes

Outcome measures of treatment effect in this review are in line with the US Food and Drug Administration (FDA) recommendation on studies of skin ulceration.²⁶ The primary outcome measure of this review is the time to ulcer healing. Secondary outcome measures of wound healing are ulcer-free time, rate or risk of ulcer recurrence and reduction in wound size. Other outcomes include wound-specific QoL, generic QoL, major adverse cardiovascular events (MACE), major adverse limb events (MALE), wound infection rate and patient-reported pain. MACE will be defined as death, myocardial infarction or stroke within 90 days of any intervention. MALE will be defined as any amputation of a limb above the ankle within 90 days of any intervention.

Search strategy and study selection

A literature search will be conducted with the support of a qualified medical librarian (TS) with predefined search terms using keywords, equivalent words and Medical Subject Headings (MESH) terms. Databases to be searched include EMBASE, OVID Medline and CINAHL from inception to October 2024. The reference lists of included studies will also be searched for other studies that may meet the inclusion criteria. Finally, a search update will be conducted prior to data analysis and any newly identified studies will be included in the final review to ensure literature saturation. A draft search strategy for OVID Medline is shown in Table 1. This strategy will be adapted for other databases.

Study screening and selection will be carried out by two reviewers independently using the web-based Covidence systematic review software (2024, Veritas Health Innovation, www.covidence.org). Authors of studies that treat AVLU patients but include other cohorts such as venous leg ulcers in the same study will be contacted so that AVLU patient data can be extracted separately. The search results will be uploaded to the software and, where the two do not agree on the inclusion of a study, consensus will be sought and, if necessary, arbitration will be provided by a third reviewer. A PRISMA chart will be used to summarise the study selection process.²⁴

Data extraction and management

Following this, two independent reviewers will commence data extraction using a dedicated Microsoft Excel spreadsheet (Microsoft® Corporation, 2022). Again, discrepancies will be resolved through consensus and, where clarification is needed, authors of included studies will be contacted. Data extraction will include study design, sample size, study population demographics, comorbidities, interventions, comparators, follow-up duration and main findings. Conflicts of interest, study funding and other sources

Table 1 Draft search strategy for OVID Medline.

1	mixed leg ulcer*.mp.
2	mixed ulcer*.mp.
3	mixed arteriovenous leg ulcer*.mp.
4	arteriovenous leg ulcer*.mp.
5	arteriovenous ulcer*.mp.
6	arterovenous leg ulcer*.mp.
7	artero venous ulcer*.mp.
8	artero-venous ulcer*.mp.
9	arterial leg ulcer*.mp.
10	arterial ulcer.mp.
11	Venous Leg Ulcer*.mp.
12	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13	revasculari?ation.mp.
14	compression.mp.
15	Compression Bandages/
16	venous treatment.mp.
17	venous ablation.mp.
18	13 or 14 or 15 or 16 or 17
19	12 and 18
20	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
21	18 and 20
22	19
23	limit 22 to (english language and humans)
24	remove duplicates from 23
25	limit 24 to (books or chapter or conference abstract or conference paper or "conference review" or editorial or erratum or letter or note)
26	24 not 25

of bias will also be reported where available. A summary table of study characteristics will be provided.

Included randomised controlled trials will be reported separately from non-randomised studies and risk assessed using the Cochrane Risk of Bias tool for randomised trials,²⁷ whereas the methodological quality of non-randomised studies will be assessed using the modified Downs and Black checklist.²⁸ Clinical heterogeneity of included studies will be considered to assess suitability for meta-analysis including patient demographics, comorbidities, types of interventions, follow-up duration and definitions used to report outcomes. If clinical homogeneity criteria are satisfied, statistical heterogeneity will be assessed using the

KEY MESSAGES

- Mixed arteriovenous ulceration is a complex condition with little evidence regarding its management
- This review aims to analyse available literature and identify the effective treatment strategies for AVLU
- We hope to use the results of this review to inform current practice and future study design

χ^2 and I^2 tests. A fixed effects model meta-analysis will be performed for studies where statistical heterogeneity is $\leq 60\%$, and for those $>60\%$ a random effects model will be used. There are no planned subgroup analyses. Dichotomous outcomes will be presented in a forest plot with risk ratios and 95% CI, whereas continuous outcomes will be presented as mean difference (MD) or SMD with 95% CI. A hazard ratio with 95% CI will be provided for time-to-event data. Data that cannot be synthesised in meta-analysis will be presented in a narrative summary. The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Working Group guidelines will be used to assess the quality of synthesised evidence.²⁹

Discussion

In AVLU there can be clinical uncertainty of the relative contribution of both arterial and venous pathologies present, whether both require treatment to achieve wound healing, and in what order they should be addressed. This uncertainty leads to delays in diagnosis, treatment and ultimately wound healing and increasing morbidity and treatment costs.⁵ The management of chronic leg ulcers currently consumes a considerable amount of resources and this has been identified as an area where patient care can be improved, and better value can be gained from utilised resources. A key aspect of this involves an evidence-based approach to the care of complex patients such as those with AVLU. One review has been conducted previously in this area, although it focused only on the use of compression.³⁰ The authors identified that reduced compression is safe and promotes ulcer healing in AVLU. They did not, however, comment on the treatment of underlying venous or arterial disease, or indeed the order in which these treatments should be undertaken.³⁰ Current international guidelines have similarly not identified an optimal strategy to investigate and treat patients with AVLU, although the use of light compression is recommended.¹⁸ This review will identify and synthesise key evidence from the literature on the management of patients with AVLU and help inform future research in this area.

Conclusion

This review will be the first to assess the evidence on the complete management of AVLU, including the benefits of combinations of compression, arterial and venous interventions. The findings will be used to inform current practice, highlight gaps in the literature and

guide future research on the subject, including interventional studies.

Conflict of Interest: The authors declare that there are no conflicts of interest.

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Author contributions: All the authors have made substantial contribution to this work including conception, design, acquisition, drafting, revision and approval of the final manuscript.

Ethics and dissemination: This is a systematic review and meta-analysis of published literature data and does not require prior ethical approval. Requests for unpublished data from authors of included studies will comply with the UK General Data Protection Regulation (GDPR). We aim to disseminate the results of this study in peer-reviewed journals and conferences.

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