VenUS IV (Venous leg Ulcer Study IV) – compression hosiery compared with compression bandaging in the treatment of venous leg ulcers: a randomised controlled trial, mixed-treatment comparison and decision-analytic model

Rebecca L Ashby,[1] Rhian Gabe,[1] Shehzad Ali,[1]
Pedro Saramago,[2] Ling-Hsiang Chuang,[1]
Una Adderley,[3] J Martin Bland,[1] Nicky A Cullum,[4]
Jo C Dumville,[1]* Cynthia P Iglesias,[1]
Arthur R Kang'ombe,[5] Marta O Soares,[2]
Nikki C Stubbs[6] and David J Torgerson[1]

[1]Department of Health Sciences, The University of York, York, UK
[2]Centre for Health Economics, The University of York, York, UK
[3]School of Healthcare, The University of Leeds, Leeds, UK
[4]School of Nursing, Midwifery and Social Work, The University of Manchester, Manchester, UK
[5]Liverpool School of Tropical Medicine, Liverpool, UK
[6]St Mary's Hospital, Leeds, UK

*Corresponding author

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Scientific summary

Compression hosiery and bandaging in the treatment of venous leg ulcers

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Background

Compression is an effective and recommended treatment for venous leg ulcers. Although the four-layer bandage (4LB) is regarded as the gold standard compression system, it is recognised that the amount of compression delivered might be compromised by poor application technique. Also, the bulky nature of the bandages might reduce ankle or leg mobility and make the wearing of shoes difficult. Two-layer compression hosiery systems are now available for the treatment of venous leg ulcers. Two-layer hosiery (HH) may be advantageous, as it has reduced bulk, which might enhance ankle or leg mobility and patient adherence. Some patients can also remove and reapply HH, which may encourage self-management and could reduce costs. However, little robust evidence exists about the effectiveness of HH for ulcer healing and no previous trials have compared HH delivering 'high' compression with the 4LB.

Objectives

The objectives of this study were to (1) compare the clinical effectiveness and cost-effectiveness of HH with the 4LB in terms of time to complete healing of venous leg ulcers, cost of treatment, health-related quality of life/utility and participant concordance with treatment; (2) conduct a mixed-treatment comparison (MTC) meta-analysis of high-compression treatments for venous leg ulcers to estimate their relative effectiveness for ulcer healing; and (3) construct a decision-analytic model to assess the cost-effectiveness of high-compression treatments for venous leg ulcers.

Methods

Design

(1) A multicentred, pragmatic, two-arm, parallel, open randomised controlled trial (RCT) with equal randomisation. Trial-level cost–utility and cost-effectiveness analyses were conducted. Assessment of the primary outcome was undertaken using blinded assessment of photographs.

(2) MTC using all relevant RCTs, including data from the trial part of Venous leg Ulcer Study IV (VenUS IV).

(3) A decision-analytic Markov model utilising all available research evidence.

Setting

(1) The settings were acute and community settings (community nurse teams or services, general practitioner practices, leg ulcer clinics, tissue viability clinics or services and wound clinics) within England and Northern Ireland.

Participants

(1) Participants were eligible for inclusion within this trial if they had a venous leg ulcer, were at least 18 years of age, had an ankle–brachial pressure index of ≥ 0.8 and were willing and able to tolerate high compression.

Interventions

(1) Participants in the intervention group received HH, which consisted of an understocking and overstocking, applied according to manufacturer's instructions. The control group received the 4LB, which was applied according to standard practice. Both treatments were designed to deliver 40 mmHg

of compression at the ankle. Participants received their allocated treatment until the leg with the largest eligible venous leg ulcer (the reference ulcer) healed and treatment was no longer required, they changed treatment, or they died or were lost to follow-up.

Main outcome measures

The primary outcome measure was time to healing of the reference ulcer, as determined by blinded assessment. Secondary outcome measures were time to healing of the reference ulcer, as determined by unblinded assessment and participant concordance with treatment, ulcer recurrence, adverse events, health-related quality of life/utility and resource use.

Results

In total, 457 participants were recruited into this trial, with 230 allocated to the HH group and 227 to the 4LB group. Using a Cox proportional hazards (CPH) model to adjust for baseline ulcer area, ulcer duration and participant mobility, and with centre included as a random effect, there was no evidence of a difference between HH and the 4LB in terms of time to ulcer healing [hazard ratio (HR) 0.99, 95% confidence interval (CI) 0.79 to 1.25; $p = 0.96$]. More participants in the HH group (39.3%) changed from their allocated trial treatment than in the 4LB group (27.8%; $p = 0.01$). Increasing age and previous reporting of a non-serious adverse event (NSAE) were also significant predictors of treatment change. Following healing of the reference leg, participants in the HH group demonstrated fewer ulcer recurrences than those in the 4LB group (14.4% vs. 23.3%; $p = 0.035$). A CPH model adjusted for baseline ulcer duration, ulcer area and participant mobility, both with and without shared centre frailty effects, also showed that time ulcer recurrence was significantly shorter in the 4LB group (HR = 0.56, 95% CI 0.33 to 0.94; $p = 0.026$). There was no statistically significant difference in the number of adverse events between groups but significantly more participants in the HH group reported one or more NSAEs during the trial (70.0% vs. 58.0%; $p = 0.050$). Adjusted health-related quality of life (as measured by the Short Form questionnaire-12 items) over 12 months' follow-up was also similar in both groups. In terms of cost-effectiveness, the mean annual cost of HH per participant was £302.4 (bias corrected 95% CI −£716.3 to £96.5) less than that for the 4LB. Participants in the HH group also had higher quality-adjusted life years (QALYs) than those allocated to the 4LB (annual difference in adjusted QALYs of 0.034, 95% bias corrected CI −0.0005 to 0.0778). Using QALYs as the measure of benefit, compression hosiery had a > 95% probability of being the most cost-effective treatment based on this within-trial analysis.

(2) The MTC suggested that the two-layer bandage (2LB) (two-component system, with a top component that is a cohesive bandage) had the highest probability of healing compared with other high-compression treatments. However, this evidence is categorised as low to very low quality.

(3) The cost-effectiveness model results suggested that the 2LB had the highest probability of being the most cost-effective high-compression treatment for venous leg ulcers. However, evidence regarding this treatment was limited. Value-of-information analysis suggested that further research that might resolve existing uncertainties was likely to be worthwhile.

Conclusions

Trial data from VenUS IV found no evidence of a difference in ulcer healing for HH and 4LB treated venous leg ulcers. However, there was evidence that HH may reduce ulcer recurrence rates when compared with the 4LB and be a cost-effective treatment. We note that, when compared with the 4LB, more patients may wish to change from HH treatment, especially older patients.

In additional analyses (MTC meta-analysis and cost-effectiveness modelling) that considered all high-compression treatments, the 2LB was shown to have the highest probability of being clinically effective and cost-effective. However, these findings must be considered in light of contributing evidence for this treatment, which is sparse and poor in some cases. Any possible guidance made at national and/or local level regarding changes to practice should take estimate quality into account.

Implications for health care

Two-layer hosiery is as effective as the 4LB in healing venous leg ulcers, although more patients may change from this treatment during the course of their ulcer episode. Patients wearing two-layer compression hosiery received fewer nurse consultations and it appears to be a more cost-effective treatment for venous ulcers than the 4LB.

Participants in the HH group also demonstrated lower rates of ulcer recurrence than those in the 4LB group; an interesting finding, which we are not able to fully explain. It may be that patients who wear HH as an ulcer treatment are more likely to wear compression stockings for secondary prevention after healing (and may wear higher compression); we are unable to confirm this hypothesis using the trial data.

Two-layer hosiery that delivers 40 mmHg pressure at the ankle can be considered as an effective alternative to the 4LB; it has the additional benefit of appearing to reduce recurrence rates and being more cost-effective. Although HH is not suitable for all patients (if they are unable to apply it or remove it for example) it does appear to offer some advantages over the 4LB.

Although all current evidence suggests that the 2LB may be an effective and cost-effective treatment for venous leg ulcers, this conclusion is associated with significant uncertainty, as the existing evidence comprises small and low-quality trials.

Implications for future research

The cost-effectiveness analysis demonstrated that VenUS IV was worthwhile, as it determined the value of HH in treating active venous ulceration. The value of further information analysis showed that the inclusion of VenUS IV considerably reduced the consequences of decision uncertainty.

However, the findings of these analyses also highlight how tentative the findings are which support the use of 2LB, and the impact of considering such low-quality findings in deciding which treatment should be used in clinical practice. Further research should thus focus on establishing, in a high-quality trial, the effectiveness of this compression system in particular.

Trial registration

This trial is registered as ISRCTN49373072.

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Editorial contact: nihredit@southampton.ac.uk

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