VenUS III: an RCT of therapeutic ultrasound in the management of venous leg ulcers

VenUS III: a randomised controlled trial of therapeutic ultrasound in the management of venous leg ulcers

JM Watson,[1] AR Kang'ombe,[1] MO Soares,[1] L-H Chuang,[1] G Worthy,[2] JM Bland,[3] C Iglesias,[1] N Cullum,[1] D Torgerson[1] and EA Nelson,[1]* on behalf of the VenUS III team

[1]Department of Health Sciences, University of York, York, UK
[2]Clinical Trials Research Unit, University of Leeds, Leeds, UK
[3]St George's Hospital Medical School, London, UK

*Corresponding author

Executive summary

Health Technology Assessment 2011; Vol. 15: No. 13
DOI: 10.3310/hta15130

Health Technology Assessment
NIHR HTA programme
www.hta.ac.uk

Executive summary

Objectives

To compare the clinical effectiveness and cost-effectiveness of low-dose ultrasound delivered in conjunction with standard care against standard care alone in the treatment of hard-to-heal venous ulcers.

Methods

Design

A multicentre, pragmatic, parallel, two-armed randomised controlled trial with an economic evaluation. Allocation was concealed, treating nurses and patients were aware of allocation, and outcome assessment was by treating-nurse report confirmed by blinded review of photographs at healing and 7 days later.

Setting

Community nurse services; community leg ulcer clinics; hospital outpatient leg ulcer clinics, among both urban and rural settings in England, Scotland, Northern Ireland and Ireland.

Participants

Patients were eligible to participate in the trial if they presented with a venous leg ulcer of >6 months' duration or $>5\,cm^2$ and an ankle–brachial pressure index of ≥ 0.8.

Interventions

Participants in the intervention group received low-dose ultrasound ($0.5\,W/cm^2$) delivered at 1 MHz, pulsed pattern of 1 : 4, applied to periulcer skin (via a water-based contact gel) weekly for up to 12 weeks alongside standard care. Standard care consisted of low-adherent dressings and compression therapy, renewed as recommended by the patient's nurse and modified if required to reflect changes in ulcer and skin condition. The ultrasound machines output was checked every 3 months to confirm intervention fidelity.

Main outcome measures

The primary end point was time to healing of the largest eligible ulcer (called the reference ulcer). Secondary outcomes were: time to healing of all ulcers, proportion of patients healed, percentage and absolute change in ulcer size, proportion of time patients were ulcer free (incorporating recurrence rates), cost of treatments, health-related quality of life (HRQoL), adverse events, withdrawal and loss to follow-up. Cost-effectiveness and cost–utility analyses were also undertaken alongside the trial.

Results

There was no statistically significant difference in the time to healing of the reference leg ulcer between the two groups (log-rank statistic 0.2544, $p = 0.6140$). The median time to reference leg ulcer healing was inestimable. There was a small, and statistically not significant, difference in the median time to complete ulcer healing of all ulcers in favour of standard care [median 328 days, 95% confidence interval (CI) 235 days, inestimable] compared with ultrasound (median

365 days, 95% CI 224 days, inestimable). There was no statistically significant difference between groups in the proportion of patients with ulcers healed at 12 months (72/168 in ultrasound vs 78/169 standard care, Fisher's exact test, $p = 0.3854$), nor in the change in ulcer area at 4 weeks. There was no evidence of a difference in recurrence of healed ulcers and few people had a recurrence within trial follow-up.

There was no difference in HRQoL [measured using the Short Form questionnaire-12 items (SF-12)] between the two groups. There were more adverse events with ultrasound than with standard care, and those events reported were consistent with those observed in other leg ulcer trials. Ultrasound therapy as an adjuvant to standard care was found not to be a cost-effective treatment when compared with standard care. The mean cost of ultrasound was £197.88 (bias-corrected 95% CI –£35.19 to £420.32) *higher* than standard care per participant per year. There was a significant relationship between ulcer healing and area and duration at baseline. In addition, those centres with high recruitment rates had the highest healing rates. The number of adverse events was significantly associated with the treatment received, with more episodes in the ultrasound group than in the standard care group. This large trial failed to find any evidence that ultrasound aided healing in this group, in contrast to earlier, smaller studies with methodological weaknesses and less effective standard care. We cannot exclude the possibility that ultrasound at other regimens might be effective, but the present evidence for ultrasound, based on the total available evidence, is not suggestive of any effects.

Conclusions

Low-dose ultrasound, delivered weekly during dressing changes, added to the package of current best practice (dressings, compression therapy), did not increase ulcer healing rates, affect quality of life (QoL) or reduce recurrence in people with hard-to-heal ulcers. Ultrasound was associated with higher costs and more adverse events. We did, however, confirm earlier findings that baseline ulcer area and ulcer duration were statistically significant predictors of time to healing, with larger ulcers and those of a longer duration taking longer to heal.

Implications for health care

There is no evidence that adding low-dose ultrasound, delivered weekly for 12 weeks, to standard care for 'hard-to-heal' ulcers aids healing, improves QoL or reduces recurrence. It increases costs and the number of adverse events.

Recommendations for future research

We identified a large variation in healing rates according to trial centres, with those centres recruiting more patients to the trial having higher healing rates overall. We controlled for ulcer area and duration; hence, the difference in healing rates across centres is not likely to be due to these prognostic factors being distributed differently across sites (i.e. larger/old ulcers in one site). The relationship between ulcer healing rates and patient recruitment is worthy of further study.

Study registration

This trial is registered as ISRCTN21175670.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Publication

Watson JM, Kang'ombe AR, Soares MO, Chuang L-H, Worthy G, Bland JM, *et al*. VenUS III: a randomised controlled trial of therapeutic ultrasound in the management of venous leg ulcers. *Health Technol Assess* 2011;**15**(13).

How to obtain copies of this and other HTA programme reports

An electronic version of this title, in Adobe Acrobat format, is available for downloading free of charge for personal use from the HTA website (www.hta.ac.uk). A fully searchable DVD is also available (see below).

Printed copies of HTA journal series issues cost £20 each (post and packing free in the UK) to both public **and** private sector purchasers from our despatch agents.

Non-UK purchasers will have to pay a small fee for post and packing. For European countries the cost is £2 per issue and for the rest of the world £3 per issue.

How to order:

– fax (with **credit card details**)
– post (with **credit card details** or **cheque**)
– phone during office hours (**credit card** only).

Additionally the HTA website allows you to either print out your order or download a blank order form.

Contact details are as follows:

Synergie UK (HTA Department)
Digital House, The Loddon Centre
Wade Road
Basingstoke
Hants RG24 8QW

Email: orders@hta.ac.uk

Tel: 0845 812 4000 – ask for 'HTA Payment Services' (out-of-hours answer-phone service)

Fax: 0845 812 4001 – put 'HTA Order' on the fax header

Payment methods

Paying by cheque
If you pay by cheque, the cheque must be in **pounds sterling**, made payable to *University of Southampton* and drawn on a bank with a UK address.

Paying by credit card
You can order using your credit card by phone, fax or post.

Subscriptions

NHS libraries can subscribe free of charge. Public libraries can subscribe at a reduced cost of £100 for each volume (normally comprising 40–50 titles). The commercial subscription rate is £400 per volume (addresses within the UK) and £600 per volume (addresses outside the UK). Please see our website for details. Subscriptions can be purchased only for the current or forthcoming volume.

How do I get a copy of *HTA on DVD*?

Please use the form on the HTA website (www.hta.ac.uk/htacd/index.shtml). *HTA on DVD* is currently free of charge worldwide.

The website also provides information about the HTA programme and lists the membership of the various committees.

NIHR Health Technology Assessment programme

The Health Technology Assessment (HTA) programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The research findings from the HTA programme directly influence decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC). HTA findings also help to improve the quality of clinical practice in the NHS indirectly in that they form a key component of the 'National Knowledge Service'.

The HTA programme is needs led in that it fills gaps in the evidence needed by the NHS. There are three routes to the start of projects.

First is the commissioned route. Suggestions for research are actively sought from people working in the NHS, from the public and consumer groups and from professional bodies such as royal colleges and NHS trusts. These suggestions are carefully prioritised by panels of independent experts (including NHS service users). The HTA programme then commissions the research by competitive tender.

Second, the HTA programme provides grants for clinical trials for researchers who identify research questions. These are assessed for importance to patients and the NHS, and scientific rigour.

Third, through its Technology Assessment Report (TAR) call-off contract, the HTA programme commissions bespoke reports, principally for NICE, but also for other policy-makers. TARs bring together evidence on the value of specific technologies.

Some HTA research projects, including TARs, may take only months, others need several years. They can cost from as little as £40,000 to over £1 million, and may involve synthesising existing evidence, undertaking a trial, or other research collecting new data to answer a research problem.

The final reports from HTA projects are peer reviewed by a number of independent expert referees before publication in the widely read journal series *Health Technology Assessment*.

Criteria for inclusion in the HTA journal series

Reports are published in the HTA journal series if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The research reported in this issue of the journal was commissioned by the HTA programme as project number 02/37/03. The contractual start date was in May 2005. The draft report began editorial review in December 2009 and was accepted for publication in July 2010. As the funder, by devising a commissioning brief, the HTA programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

The views expressed in this publication are those of the authors and not necessarily those of the HTA programme or the Department of Health.

ISSN 1366-5278 (Print)
ISSN 2046-4924 (Online)
ISSN 2046-4932 (DVD)

Published by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk), on behalf of NETSCC, HTA.
Printed on acid-free paper in the UK by the Charlesworth Group.