

Use of weekly, low dose, high frequency ultrasound for hard to heal venous leg ulcers: the VenUS III randomised controlled trial

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ABSTRACT

Objective To assess the clinical effectiveness of weekly delivery of low dose, high frequency therapeutic ultrasound in conjunction with standard care for hard to heal venous leg ulcers.

Design Multicentre, pragmatic, two arm randomised controlled trial.

Setting Community and district nurse led services, community leg ulcer clinics, and hospital outpatient leg ulcer clinics in 12 urban and rural settings (11 in the United Kingdom and one in the Republic of Ireland).

Participants 337 patients with at least one venous leg ulcer of >6 months' duration or >5 cm² area and an ankle brachial pressure index of ≥0.8.

Interventions Weekly administration of low dose, high frequency ultrasound therapy (0.5 W/cm², 1 MHz, pulsed pattern of 1:4) for up to 12 weeks plus standard care compared with standard care alone.

Main outcome measures Primary outcome was time to healing of the largest eligible leg ulcer. Secondary outcomes were proportion of patients healed by 12 months, percentage and absolute change in ulcer size, proportion of time participants were ulcer-free, health related quality of life, and adverse events.

Results The two groups showed no significant difference in the time to healing of the reference leg ulcer (log rank test, P=0.61). After adjustment for baseline ulcer area, baseline ulcer duration, use of compression bandaging, and study centre, there was still no evidence of a difference in time to healing (hazard ratio 0.99 (95% confidence interval 0.70 to 1.40), P=0.97). The median time to healing of the reference leg ulcer was inestimable. There was no significant difference between groups in the proportion of participants with all ulcers healed by 12 months (72/168 in ultrasound group v 78/169 in standard care group, P=0.39 for Fisher's exact test) nor in the change in ulcer size at four weeks by treatment group (model estimate 0.05 (95% CI -0.09 to 0.19)). There was no difference in time to complete healing of all ulcers (log rank test, P=0.61), with median time to healing of

328 days (95% CI 235 to inestimable) with standard care and 365 days (224 days to inestimable) with ultrasound. There was no evidence of a difference in rates of recurrence of healed ulcers (17/31 with ultrasound v 14/31 with standard care, P=0.68 for Fisher's exact test).

There was no difference between the two groups in health related quality of life, both for the physical component score (model estimate 0.69 (-1.79 to 3.08)) and the mental component score (model estimate -0.93 (-3.30 to 1.44)), but there were significantly more adverse events in the ultrasound group (model estimate 0.30 (0.01 to 0.60)). There was a significant relation between time to ulcer healing and baseline ulcer area (hazard ratio 0.64 (0.55 to 0.75)) and baseline ulcer duration (hazard ratio 0.59 (0.50 to 0.71)), with larger and older ulcers taking longer to heal. In addition, those centres with high recruitment rates had the highest healing rates.

Conclusions Low dose, high frequency ultrasound administered weekly for 12 weeks during dressing changes in addition to standard care did not increase ulcer healing rates, affect quality of life, or reduce ulcer recurrence.

Trial registration ISRCTN21175670 and National Research Register N0484162339

INTRODUCTION

Leg ulceration is a chronic, recurring condition that affects 1.5–1.8% of adults in industrialised countries¹ (with venous leg ulcers representing up to 84% of leg ulcers²) and has a considerable impact on health and quality of life.^{2,3} High compression bandaging is effective treatment,⁴ healing most new venous leg ulcers (<6 months' duration) within a year.⁵ The priority is now to increase healing in ulcers with poorer prognostic profiles (bigger and older ulcers).

Ultrasound therapy is a standard treatment option for soft tissue injuries in physiotherapy clinics, and it is used in some centres for the management of chronic wounds⁶ and is recommended in some clinical practice guidelines.^{7–9} It is thought that using low intensity

ultrasound ($\leq 3 \text{ W/cm}^2$) can be used to stimulate normal physiological responses to injury to aid repair.¹⁰ Other ultrasound regimens, delivered in a water bath, have been used with the primary aim of debriding wounds.¹¹

A systematic review of trials of ultrasound therapy for treating venous leg ulcers suggested that it improved healing.¹² Meta-analysis of the four trials that reported data on complete ulcer healing at 8–12 weeks produced a relative risk for healing of 1.44 (95% confidence interval 1.01 to 2.05). However, the trials identified were methodologically weak, heterogeneous, prone to bias, and varied widely in application regimens.

To investigate this further, we conducted a randomised controlled trial to compare the effect of standard ulcer care alone with standard care plus ultrasound treatment. We measured time to healing of the reference ulcer, health related quality of life, proportion of participants with ulcers healed at 12 months, percentage and absolute change in ulcer size, adverse events, and cost of treatments. The economic evaluation is reported separately.¹³

METHODS

Ultrasound treatment

The dose at which ultrasound is delivered is related to its frequency (hertz), power (watts), pulsed or continuous cycle, and the duration of the treatment, which can produce many possible combinations.¹⁴ Therapeutic ultrasound has a frequency of 0.75–3.0 megahertz (MHz), and most machines used to deliver it are set at a frequency (that is, cycles per second) of either 1 or 3 MHz.¹⁵ The total amount of energy in an ultrasound beam is expressed in watts (W) indicating its power.¹⁵

At the time our study was designed, most evidence was available for ultrasound treatment at a frequency of 1 MHz and dose of 0.5 W/cm^2 (including the one study in the systematic review with only moderate risk of bias). Previous trials had evaluated ultrasound administered weekly, two or three times a week, or with declining frequency of administration. Administering ultrasound requires bandage removal, and hence our choice of treatment regimen balanced the costs of these visits against the potential reduction in healing time (if ultrasound were effective). We therefore chose a low dose, high frequency ultrasound treatment (1 MHz at 0.5 W/cm^2) with a pulse pattern set at 1:4 and the duration of each treatment being determined by ulcer area. Treatment was delivered once weekly for up to 12 weeks.

Participants and setting

This was a pragmatic, multicentre, two arm, randomised controlled, open trial with equal randomisation carried out in 11 centres in the United Kingdom and one in the Republic of Ireland. Participants were recruited between March 2006 and December 2008 (end of extended recruitment period) from services led by community and district nurses, community leg ulcer clinics, and hospital outpatient leg ulcer clinics in

urban and rural settings. Centres were recruited through staff from our known community of leg ulcer services and clinics. All venous leg ulcer patients on the treatment lists within these centres were assessed for trial inclusion by completion of a screening form by either their usual nursing team or a study research nurse. Systematic methods were used to approach and potentially recruit participants.

Nurse training

Before the trial started, participating nurses attended a training day in their centre which covered the rationale for the study, patient eligibility, recruitment and consent procedures, data collection, adverse event reporting, and the ultrasound application technique according to the manufacturer's instructions and clinical expertise. Competency in ultrasound application was assessed at the end of the training. Trained nurses were permitted to train other local nurses to allow treatments to be maintained during staff absences. Continual support was available from the trial coordinator. Treatment fidelity checks were not undertaken.

This model of training reflected the likely investment in training that would be available in the National Health Service if the intervention proved successful and was rolled out to community nursing services and hospital outpatients. To maintain the pragmatic nature of the trial, we did not impose a regimen of observation of practice greater than there would be in standard care.

Patient eligibility

Eligible participants had venous leg ulcers of >6 months' duration or >5 cm² in size, or both. A participant was considered to have a venous leg ulcer if there was no other evident cause and clinical assessment suggested it was venous (moist, shallow, irregular shape, venous eczema, ankle oedema, lipodermatosclerosis, not confined to the foot) and participants had had an ankle brachial pressure index of ≥ 0.8 within the past three months. If participants had more than one ulcer, the largest eligible ulcer was defined as the reference ulcer, which would be followed throughout the study and, if allocated, receive the ultrasound therapy.

We originally planned to recruit only those able to tolerate high compression bandages. However, clinical collaborators argued that those who can tolerate only reduced compression therapy represent a particular challenge to treat and might benefit in particular from any effect of therapeutic ultrasound. We therefore removed the inclusion criterion of "willing and able to wear four-layer high compression bandaging."

Participants were excluded if their leg ulcer was due to other causes, they were of childbearing age, were allergic to ultrasound contact gel, had poorly controlled diabetes ($\text{HbA}_{1c} > 10\%$ measured within the past three months), or had any of the known contraindications to ultrasound (including ankle or knee prosthesis or metal in the lower leg, suspected thrombophlebitis, active cellulitis, and suspected or

confirmed local cancer or metastatic disease). The original protocol also stated the study would not recruit people with rheumatoid arthritis, peripheral arterial disease, or diabetes. However, after discussions with clinical collaborators, the first two criteria were removed as unnecessary, and the last was replaced by “poorly controlled diabetes.”

Ethical approval was gained for all changes. Participants gave written, informed consent.

Patient randomisation

Those patients deemed potentially eligible according to the screening form were seen by one of the trained nurses, who explained the study, confirmed eligibility, and obtained written consent. Consenting patients were randomised to receive ultrasound plus standard care or standard care alone. Randomisation was performed by the nurses telephoning an independent, secure, remote, randomisation service (York Trials Unit) thereby concealing treatment allocation. Randomisation was carried out by permuted block design with varying block sizes of four and six. Because of the nature of the intervention, it was not possible to blind either the patient or the nurse to the treatment.

Intervention

The ultrasound therapy was applied with a SoLo Therasonic 355 machine (EMS Physio, Wantage, UK). Before use, all the trial machines were tested by the National Physical Laboratory (Teddington, UK). Measurements were made of total acoustic power and effective radiating area, and these were within the tolerance of $\pm 20\%$ specified by IEC 60601-2-5 and IEC 61689. The machines were serviced regularly throughout the trial.

Treatment was given weekly at the patients' regular dressing changes. After removal of all dressings and bandaging, the wound was cleaned as usual. The ultrasound transducer head was sterilised with alcohol wipes. Ultrasound was then applied to the skin surrounding the reference ulcer, using a water based contact gel recommended by the manufacturer, for 5–10 minutes by moving the transducer head in a slow, controlled manner around the edges of the ulcer in overlapping circles to cover the skin evenly. Ulcers of area $< 5 \text{ cm}^2$ received ultrasound for five minutes, those of $\geq 10 \text{ cm}^2$ received 10 minutes' ultrasound. For ulcers between 5 cm^2 and 10 cm^2 , treatment time in minutes equalled the ulcer area in cm^2 (ulcer of 6 cm^2 area = 6 minutes' treatment). After treatment, all traces of the contact gel were removed and the transducer head was cleaned with alcohol wipes. After the 12 weeks of ultrasound, participants returned to standard care alone.

Treatment before study enrolment was not formally recorded, but standard care comprised low adherent dressings and four-layer bandaging that was high compression, reduced compression, or no compression, depending on the patient's tolerance, replaced at each weekly visit. Changes to this regimen, as deemed appropriate by the treating clinician, were recorded. Since

standard care also reflected treatment as usual according to local practice, it could vary between centres.

Outcome measurement

The primary outcome was time to complete healing of the reference ulcer. Ulcer healing was defined as full epithelial cover without scab. Digital photographs of the reference ulcer were taken every four weeks, at point of healing, and seven days after healing by the treating nurse. Photographs were assessed by two remote, independent assessors who were blind to treatment allocation to determine the date of healing and to protect the study against assessment biases. Any discrepancies were referred to a third assessor. The primary outcome was calculated using the date of healing as decided by the blinded assessors. However, if no photographs were available for a patient, then the date of healing decided by the treating nurse was taken as the healed date.

Secondary outcomes (not all reported here but in our economic evaluation¹³) included the proportion of patients with ulcers healed at three, six, and 12 months, proportion of time ulcer-free, change in ulcer area, recurrence rates, health related quality of life, and adverse events. Ulcer area was calculated every four weeks (before ultrasound delivery) by the nurse tracing the perimeter on an acetate grid with a fine-nibbed pen, following a standard method that is accurate and reliable.¹⁶ As leg ulcer care is most commonly delivered in the home, it was not feasible to have

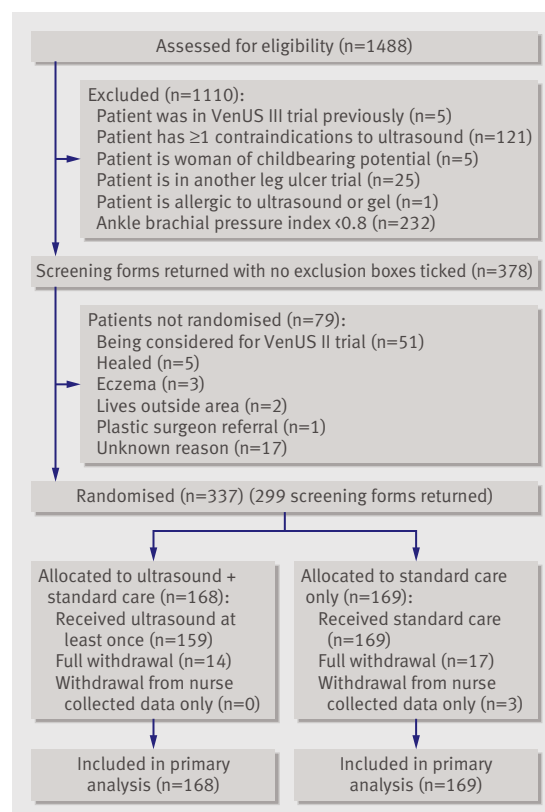


Fig 1 | Flow of participants through trial

Table 1 | Baseline characteristics of 337 patients with venous leg ulcers who were randomised to standard care alone or to ultrasound plus standard care. Values are numbers (percentages) unless stated otherwise

Characteristic	Standard care (n=169)	Ultrasound (n=168)	Overall (n=337)
Men	73 (43)	64 (38)	137 (41)
Women	96 (57)	104 (62)	200 (59)
Age (years):			
Mean (SD)	69.92 (14.21)	68.91 (14.80)	69.44 (14.50)
Median (range)	71.91 (20–98)	71.64 (26–95)	71.85 (20–98)
Reference ulcer area (cm ²):			
Mean (SD)	27.18 (41.96)	27.95 (44.47)	27.56 (43.17)
Median (range)	12.0 (1.0–283.5)	12.0 (1.0–268.0)	12.0 (1.0–283.5)
Reference ulcer duration (months):			
≤6	56 (33)	42 (25)	98 (29)
>6	113 (67)	126 (75)	239 (71)
Oldest ulcer duration (months):			
Mean (SD)	33.58 (56.38)	33.93 (66.91)	33.75 (61.76)
Median (range)	11 (0–36)	12 (0–516)	12 (0–516)
High compression bandaging used:			
Yes	148 (88)	145 (86)	293 (87)
No	21 (12)	23 (14)	44 (13)
ABPI of reference limb:			
Mean (SD)	1.08 (0.21)	1.06 (0.19)	1.07 (0.20)
Median (range)	1.10 (0.08–1.64)	1.06 (0–1.69)	1.08 (0–1.69)

ABPI=ankle brachial pressure index.

a nurse blinded to the treatment attend dressing changes to trace the ulcer. Tracing data were measured using a computer package (Mouseeyes).¹⁷

Patients' perceptions of health outcome were assessed with the short form 12 (SF-12), which is sensitive to changes in venous ulcer healing status.¹⁸ Questionnaires were administered by post at three, six, nine, and 12 months.

Serious adverse events were defined as death, life threatening risk, hospitalisation, persistent or substantial disability or incapacity, and other medically important conditions (such as being newly diagnosed with diabetes). Other adverse events were classed as non-serious. Reporting nurses indicated whether, in their opinion, the event was related to the trial treatment. A list of possible treatment related adverse events was established a priori, based on the literature and the VenUS I and II trials^{5,19} (including pressure damage, infection, new ulcer, and ulcer deterioration).

Statistical analysis

All analyses were done in SAS version 9.1 and STATA version 10 on an intention to treat basis with a two sided 5% significance level. Scoring of the SF-12 questionnaire's health related quality of life was done with the QualityMetric Health Outcomes Scoring Software 2.

Allowing for 10% attrition, we estimated that a total of 336 participants would provide 90% power to detect a reduction in the median time to healing from 22 weeks to 15 weeks. The control healing time was based on trial data for large or chronic ulcers: 13–37% of people with chronic and large ulcers heal at

24 weeks with high compression.²⁰ Our target population included people with chronic or large ulcers, and from previous trials,⁵ we estimated that about 50% of ulcers in the standard care group would heal within 22 weeks. As ultrasound increases treatment time and is not currently used by community nurses, we anticipated that clinicians would require a moderate effect size for them to adopt this technology; hence a reduction in healing time from 22 to 15 weeks was deemed clinically meaningful. The minimum clinically important effect size is related to the ease of delivery of the intervention, its acceptability, and costs, both in initiation and ongoing delivery.

Our primary analysis compared time to complete healing of the reference ulcer between the two randomised groups using a Cox regression model.²¹ Shared centre frailty (random) effects were assumed to follow a γ distribution, and STATA was used to fit a Cox survival regression model. The analysis adjusted for centre as a random effect, ulcer area (from baseline tracing), ulcer duration, and whether the patient was treated with high compression bandaging (as fixed effects). These factors were chosen because they had been prognostic in other leg ulcer studies.^{5,19} The distribution of baseline ulcer area and baseline ulcer duration were highly skewed, so we used the logarithm of baseline ulcer area and ulcer duration in the subsequent analysis. Patients who withdrew from the study or whose reference ulcer had not healed by trial conclusion were treated as censored. If centres recruited five or fewer patients we repeated the analysis with no adjustment for centre as a sensitivity analysis.

The assumption of proportional hazards was checked by using log-log plots, by including interaction terms in the model (for each term with time), and by looking at plots of Schoenfeld residuals. Kaplan-Meier survival curves describing time to healing were produced for the two groups and the median time to healing with 95% confidence interval.

Cohen's κ measure of inter-rater agreement was used to assess agreement between the two assessors of the photographs for healing. This was repeated to look at agreement between the final decision from the photograph assessment and the nurses' date of healing. Ulcer area at week 4 was compared between treatment groups using analysis of covariance to adjust for baseline ulcer area, centre, ulcer duration, and use of compression bandaging.

We analysed the scores for the physical and mental health components of the SF-12 questionnaire using a multi-level regression model. The outcomes at each time point were used in a single model, with time points nested within participants to account for within-patient correlation in scores. The model was used to estimate the difference between treatments over the whole 12 month follow-up. The outcome modelled was the score at each follow-up assessment, and the covariates included in the model were centre, baseline ulcer area, ulcer duration, use of compression, and time (indicators for 0, 3, 6, 9 and 12 months). We assessed whether the pattern in quality of life scores over time was

Table 2 | Treatment details for 337 patients with venous leg ulcers who were randomised to standard care alone or to ultrasound plus standard care

	Standard care (n=169)	Ultrasound (n=168)
Total No (%) of bandages applied:	6473 (100)	8013 (100)
Four layer high compression	2241 (35)	2151 (27)
Three layer high compression	1543 (24)	2325 (29)
Three layer reduced compression	668 (10)	1063 (13)
Two layer high compression	857 (13)	921 (11)
Short stretch compression	805 (12)	848 (11)
Low compression	139 (2)	250 (3)
No compression	220 (3)	455 (6)
No of ultrasound applications per person:		
Mean (SD)	—	10.25 (2.96)
Median (range)	—	11 (1–15)
No (%) of participants with missing values	—	9 (5)
Proportion of consultations where ultrasound applied:		
Mean (SD)	—	0.77 (0.24)
Median (range)	—	0.86 (0.14–1.00)
No (%) of participants with missing values	—	9 (5)
Total duration of ultrasound applications per person (minutes):		
Mean (SD)	—	73.94 (31.69)
Median (range)	—	69.0 (9.0–130.0)
No (%) of participants with missing values	—	9 (5)

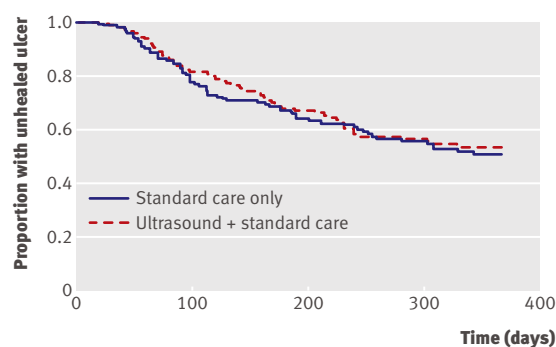
different between the two treatments by including an interaction term between treatment and time in the model.

We assessed the assumption of normally distributed data and, if necessary, used log transformations or other analysis methods.

We used a negative binomial model²² adjusting for the same covariates as the primary analyses, to compare the average number of adverse events experienced by each patient in the two treatment groups. Separate analyses were performed for serious and non-serious adverse events.

RESULTS

Between January 2006 and December 2008, 1488 people with leg ulcers were screened across 12 centres, and 337 (22.6%) were randomised: 168 to ultrasound plus

**Fig 2** | Kaplan-Meier survival curve for time to healing of reference ulcers among 337 patients with venous leg ulcers randomised to standard care alone or to ultrasound plus standard care

standard care and 169 to standard care. Figure 1 shows the flow of participants through the trial, and table 1 summarises their baseline characteristics.

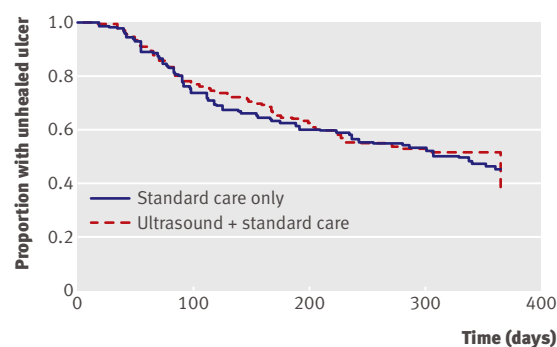
Table 2 gives details of the compression bandaging provided, for both groups, and the ultrasound treatment for the intervention group. Participants in the ultrasound group had a median of 11 ultrasound treatments during the 12 week ultrasound period (mean 10.25).

Primary outcomes

We found no evidence of a difference in time to healing between the two treatment groups with either the log rank test (log rank test statistic 0.25, $P=0.61$) or Wilcoxon's rank sum test (Wilcoxon test statistic 0.33, $P=0.56$). Figure 2 shows the Kaplan-Meier survival curve for time to healing of reference ulcers in both groups.

For the Cox model, the proportional hazard assumption was tested and was not violated, either separately for each covariate (ultrasound *v* standard care ($P=0.7230$), log(area) ($P=0.1467$), log(duration) ($P=0.2938$), high compression ($P=0.2030$)) or globally ($P=0.3548$). Hence, all hazard ratios were assumed constant during the follow-up period. From the Cox proportional hazards model, after adjustment for baseline ulcer area, baseline ulcer duration, use of compression bandaging, and study centre (as a random effect), there was still no evidence of a difference in time to healing between the two treatment groups (hazard ratio 0.99 (95% confidence interval 0.70 to 1.40), $P=0.97$). There was, however, significant heterogeneity in the healing rates among centres ($P=0.0001$) not explained by the covariates included in the model. We found that centres recruiting more participants were associated with higher healing rates than centres recruiting fewer participants.

The median time to complete healing of all ulcers in the standard care group was 328 days (95% confidence interval 235 days to inestimable) and in the ultrasound group was 365 days (224 days to inestimable). Figure 3 shows the Kaplan-Meier survival curve for time to complete healing of all ulcers in both groups.

**Fig 3** | Kaplan-Meier survival curve for time to complete healing of all ulcers among 337 patients with venous leg ulcers randomised to standard care alone or to ultrasound plus standard care

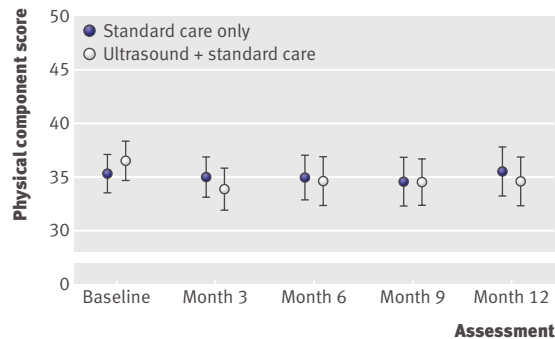


Fig 4 | Mean physical component summary score of the short form 12 (SF-12) questionnaire among 337 patients with venous leg ulcers randomised to standard care alone or to ultrasound plus standard care

Secondary outcomes

There was no significant difference between the two groups in the proportion of participants with all ulcers healed (according to the nurse forms) by 12 months (72/168 in ultrasound group *v* 78/169 in standard care group, $P=0.3854$ for Fisher's exact test). For comparison with other studies, there was no difference in the proportions of reference ulcers healed (according to blinded assessment of photographs) at three months (28/168 *v* 30/169 standard care, $P=0.8854$) or at six months (48/168 *v* 52/169, $P=0.7208$).

We used Cohen's κ measure to assess the agreement between the two blinded assessors of the ulcer photographs and whether the assessors agreed with the unblinded nurse as to whether the reference ulcer had healed. The photograph assessors' measure of agreement was estimated as 0.84 (95% confidence interval 0.78 to 0.90), and agreement between the assessors and the nurse was 0.76 (0.69 to 0.83).

Of the 133 participants with photographically confirmed healing of their reference ulcer, 124 were successfully contacted later to ascertain whether their ulcer had recurred. The remaining participants were not contacted for various reasons (including invalid or changed telephone number, telephone not answered, and patient moved). Overall, the reference ulcer had recurred in 31 (25%) of the 124 participants (14 (45%) from the standard care group, 17 (55%) from the ultrasound group). There was no significant difference in the recurrence rates between the two groups ($P=0.68$ for Fisher's exact test).

We analysed ulcer area after four weeks of treatment to determine whether ultrasound affected rate of healing (baseline ulcer area was included in the model as a covariate). There was a non-significant ultrasound treatment effect (model estimate 0.05 (95% CI -0.09 to 0.19), $P=0.50$) and a non-significant ulcer compression effect (model estimate 0.02 (-0.19 to 0.24), $P=0.84$). Baseline ulcer area and duration both had significant effects on the initial change in ulcer area (model estimates 0.77 (0.72 to 0.84) and 0.13 (0.07 to 0.19) respectively, both $P=0.0001$): smaller and newer ulcers reduced in area more quickly. There was no

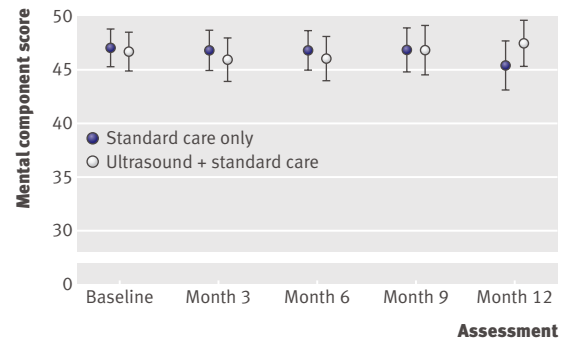


Fig 5 | Mean mental component summary score of the short form 12 (SF-12) questionnaire among 337 patients with venous leg ulcers randomised to standard care alone or to ultrasound plus standard care

evidence of any difference between centres (model estimate 0.01, $P=0.15$).

At baseline, the mean physical component summary score of the SF-12 questionnaire was 36.55 (SD 11.32) for the ultrasound group and 35.33 (11.47) for the standard care group (compared with a score of 43.93 (9.29) for people aged 65–74 years in the general US population), and the mean mental component summary score was 46.72 (11.52) for the ultrasound group and 47.11 (11.29) for the standard care group (compared with 51.57 (8.36) for the general US population). Response rates for the SF-12 questionnaires were 89%, 84%, 81%, and 86% at three, six, nine, and 12 months respectively. Figures 4 and 5 show little change in the physical and mental component scores over time: hence there was a constant linear trend of both scores against time. There was no evidence of a difference between the two treatment groups in the mean physical component summary scores (model estimate 0.69 (-1.79 to 3.08), $P=0.58$) or the mean mental component summary scores (model estimate -0.93 (-3.30 to 1.44), $P=0.44$).

There were 88 serious adverse events in 64 participants: 29 participants (45%) in the standard care group and 35 (55%) in the ultrasound group. There were 445 non-serious adverse events in 153 participants: 67 (44%) were in the standard care group and 86 (56%) in the ultrasound group. When we set the model response as the number of serious adverse events per patient throughout follow-up, we found no significant difference in adverse events due to treatment received (model estimate 0.23 (-0.34 to 0.79), $P=0.39$) or baseline use of compression bandaging (model estimate -0.16 (-0.98 to 0.65), $P=0.66$). There was weak evidence that larger baseline ulcer area and longer baseline ulcer duration were associated with more serious adverse events (model estimates 0.19 (-0.03 to 0.40), $P=0.08$, and 0.22 (-0.02 to 0.45), $P=0.06$, respectively).

The number of non-serious adverse events was significantly associated with the treatment received, with more events in the ultrasound group than the standard care group (model estimate 0.35 (0.02 to 0.67), $P=0.04$) but was not related to baseline ulcer area (model estimate 0.05 (-0.08 to 0.17), $P=0.42$), baseline ulcer duration (model estimate 0.08 (-0.06 to 0.22), $P=0.24$), and

baseline compression use (model estimate -0.003 (-0.46 to 0.47), $P=0.99$).

DISCUSSION

We found no evidence that therapeutic low dose, high hertz frequency ultrasound delivered once a week improves the healing of venous leg ulcers. We did observe a significant centre effect, such that rates of ulcer healing differed significantly between treatment centres. A centre's healing rate was proportional to the number of participants. There was no evidence of ultrasound having an effect on healing when analysed by centre. As there was little change in the SF-12 questionnaire's physical component summary score during the trial in either group and no evidence of a significant change in the mental component summary score over time, ultrasound showed no impact on health related quality of life.

Bandaging use was recorded 6473 times for the people treated with standard care and 8013 times for the people treated with ultrasound. Were the level of compression of bandages to differ significantly between the two groups, then this might introduce a performance bias. The proportion of visits at which high compression systems (four layer, three layer, or two layer) was used was 67% (5397/8013) for ultrasound and 72% (4641/6473) for standard care. The proportion of visits at which no compression was used was 3.4% (220/6473) in standard care and 5.7% (455/8013) in the ultrasound group. The modest differences in the level of compression used (fewer in the standard care group had no compression) were not significant, and hence performance bias is unlikely to account for the lack of evidence of benefit with ultrasound.

Although there were more adverse events in the ultrasound group than the standard care group, as ultrasound is not currently used in practice, it is possible that nurses were more likely to attribute adverse events (such as ulcer deterioration) to a treatment with which they are relatively unfamiliar. The overall adverse event rate (the number of people reporting any adverse event) was similar to that in the VenUS I trial,⁵ which reported an event rate of about 40%.

Strengths and limitations of study

The strengths of this study include the large sample size, wide inclusion criteria, blinded allocation, use of best available standard treatment, blinded outcome assessment, low loss to follow-up, collection of quality of life and effectiveness data, and long duration of follow-up. Limitations included the modest response rate from patients at 12 months in respect of the quality of life questionnaires.

In addition, there is the possibility of random error in the evaluation of the ulcer area when traced using the computer software.¹⁷ However, the ulcers were measured every four weeks for the purpose of dose adjustment, and, although this was done by the unblinded nurse, there is no reason for systematic errors (bias) being introduced as the primary outcome measure was time to complete healing as assessed by a blinded

assessor. Any doubts regarding the potential errors in ulcer measurements confirm the importance of the more robust outcome measure of time to healing with the addition of a blinded outcome assessment to confirm this.

Rationale for this study

Reviews of earlier trial evidence for the effects of ultrasound in wound healing generally²³ and leg ulcers specifically¹² identified the potential benefit of ultrasound therapy for venous ulcer healing. However, a definitive study was needed since these trials were small, had methodological weaknesses, and had incomplete reporting and were at high risk of bias. Furthermore, the clinical contexts in which the trials had taken place (such as before the widespread introduction of high compression therapy) meant that their relevance to today's leg ulcer management was uncertain. Since completion of our study, an updated systematic review has been published with eight trials included, six using high frequency ultrasound and two using low frequency ultrasound.²⁴

We now know from prognostic studies and trials that high compression therapy heals some 80% of venous ulcers within 12 months and that ulcers smaller than 5 cm² and of less than six months' duration are likely to heal quickly.²⁰ In designing this trial, we therefore felt that adding an adjuvant ultrasound therapy to the treatment of small or new ulcers was unwarranted. The sample size of a trial to find a benefit of adding ultrasound to the treatment of most venous ulcers would have to be very large given the high healing rate. We therefore recruited people with hard to heal ulcers—those for whom clinicians might consider additional interventions beyond standard care. On the whole, participants' ulcers were large (12 cm²) and chronic (1 year duration), and those recruited were representative of the venous ulcer population in terms of age and sex.¹

There are two explanations for our findings: firstly, that there is a treatment effect but our trial failed to detect it (due to chance or to methodological problems), or, secondly, ultrasound therapy at the dose and frequency used does not accelerate healing of hard to heal venous ulcers. We minimised the play of chance by having a large sample size. We minimised detection bias by using confirmed healing date by photographic assessment. The possibility that ultrasound machines did not deliver the prescribed dose was reduced by having them serviced and calibrated regularly, and we recorded all treatments given to ascertain if there was evidence of performance bias (such as extra treatments in the standard care group), which there was not.

Our decision to use low dose, high frequency ultrasound therapy (0.5 W/cm², 1 MHz, pulsed pattern of 1:4) administered weekly was based on earlier evidence (the largest trial) and the need to balance the delivery of leg ulcer care in an efficient manner, with weekly visits to renew dressings and bandages, against the desire to deliver ultrasound more frequently. We

WHAT IS ALREADY KNOWN ON THIS TOPIC?

Most venous leg ulcers heal in 6–12 months, but those with a duration of >6 months or that are larger than average are harder to heal

Clinical trials have suggested that therapeutic ultrasound can help heal leg ulcers, but these studies were methodologically weak, small in size, varied widely in application regimens, included people with small, new ulcers, which heal relatively quickly, or did not use optimal existing treatments

WHAT THIS STUDY ADDS

There is no evidence of a benefit in terms of time to ulcer healing, probability of ulcer having healed at 12 months, rate of reduction in ulcer area, or health related quality of life for people with hard to heal ulcers treated with weekly administration of low dose, high frequency, adjuvant ultrasound therapy (0.5 W/cm², 1 MHz, pulsed pattern of 1:4) for up to 12 weeks

stopped delivering ultrasound at 12 weeks as we felt this was a pragmatic approach to evaluating the addition of a novel therapy that took account of the extra treatment time required by the nurse. We felt that asking nurses to apply ultrasound for the whole trial period would have resulted in disillusionment if nurses felt that there was no discernable benefit, as this would increase the workload significantly: this would have hampered recruitment. The lack of any treatment effect, as seen in the Kaplan-Meier curves, seems consistent with there being no effect on healing rate within the first 12 weeks. Given the widely accepted use of compression therapy, replaced usually once or twice a week, it would be impractical to deliver ultrasound other than at the regular bandage renewal; hence our rationale for weekly ultrasound to integrate with current practice.

Implications of results

Here we report the largest trial undertaken of therapeutic ultrasound for wound healing.^{23–25} This trial is also much larger than any trial of ultrasound for fractures included in a recent systematic review²⁶ and was conducted and reported in accordance with international guidelines for research excellence.^{27,28}

We designed this trial in 2003, when there were seven trials summarised in a systematic review,¹² two of which were not randomised. If we now add the VenUS III data into that meta-analysis (by taking our numbers of ulcers healed at 12 weeks), we find that, although more ulcers healed with ultrasound than with sham ultrasound or standard care, the difference was not statistically significant ($P=0.095$). Furthermore, VenUS III is the only trial to meet all the validity criteria of adequate randomisation, full allocation concealment, blinded outcome assessment, and analysis based on intention to treat, so we would argue that the VenUS III result is the most valid. The conclusion we therefore draw from all the evidence is that therapeutic ultrasound does not confer any benefit on the healing of hard to heal venous leg ulcers (that is, >5 cm² in area or >6 months old, or both).

However, we evaluated only one ultrasound regimen, and so our results cannot be extrapolated to other regimens, such as those delivering ultrasound

via a water bath to debride wounds. We identified a large variation in healing rates according to trial centres, with those centres recruiting more participants to the trial having higher healing rates overall. This centre effect may be a manifestation of a relation between the volume of throughput and the quality of care. This finding is worthy of further exploration. Other research questions include the evaluation of the effectiveness of this and alternative ultrasound regimens, say through value of information approaches.

Implications for clinicians are that there is no evidence to support the addition of ultrasound therapy to treatments for people with hard to heal leg ulcers.

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Contributors: EAN was the chief investigator, chaired the trial management group, and edited and approved the final draft of the paper. JMW was the trial coordinator and drafted the paper. GW and JMB designed the clinical analysis. JMB oversaw the conduct of the analysis. ARK conducted the clinical analysis. MOS contributed to the trial management group, designed the economic analyses, and oversaw the conduct of the analysis. L-HC undertook the economic analysis. CI participated in the design and conduct of the study. NC and DT contributed to the study design and coordination and commented on drafts of the paper. EAN is the guarantor of the paper.

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Data sharing: No additional data available

1 Graham ID, Harrison MB, Nelson EA, Lorimer K, Fisher A. Prevalence of lower-limb ulceration: a systematic review of prevalence studies. *Adv Skin Wound Care* 2003;16:305-16.

- 2 Dale JJ, Callam MJ, Ruckley CV, Harper DR, Berrey PN. Chronic ulcers of the leg: a study of prevalence in a Scottish community. *Health Bulletin (Edin)* 1983;41:311-4.
- 3 Briggs M, Flemming K. Living with leg ulceration: a synthesis of qualitative research. *J Adv Nurs* 2007;59:319-28.
- 4 O'Meara S, Cullum NA, Nelson EA. Compression for venous leg ulcers. *Cochrane Database Syst Rev* 2008;4:CD000265.
- 5 Iglesias C, Nelson EA, Cullum NA, Torgerson DJ, for the VenUS Team. The VenUS I Trial: a randomised comparison of 4-layer and short-stretch bandages for the treatment of venous leg ulcers. *Health Technol Assess* 2004;8:iii,1-105.
- 6 Moffatt C, Martin R, Smithdale R. *Leg ulcer management*. Blackwell Publishing Ltd, 2007.
- 7 Registered Nurses Association of Ontario (RNAO). Assessment and management of venous leg ulcers: guideline supplement. RNAO, 2007.
- 8 American Association for the Advancement of Wound Care (AAWC). Summary algorithm for venous ulcer care. AAWC, 2005.
- 9 Wound, Ostomy and Continence Nurses Society (WOCN). Guidelines for the management of wounds in patients with lower-extremity venous disease. WOCN, 2005.
- 10 Ter Haar G. Therapeutic ultrasound. *Eur J Ultrasound* 1999;9:3-9.
- 11 Tan J, Abisi S, Smith A, Burnand KG. A painless method of ultrasonically assisted debridement of chronic leg ulcers: a pilot study. *Eur Vasc Endovasc Surg* 2007;33:234-8.
- 12 Flemming K, Cullum N. Therapeutic ultrasound for venous leg ulcers. *Cochrane Database Syst Rev* 2000;4:CD001180.
- 13 Watson JM, Kang'ombe AR, Soares M, 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* [forthcoming].
- 14 Watson T. Ultrasound in contemporary physiotherapy practice. *Ultrasonics* 2008;48:321-9.
- 15 Speed CA. Therapeutic ultrasound in soft tissues lesions. *Rheumatology* 2001;40:1331-6.
- 16 Etris MB, Pribble J, LaBrecque J. Evaluation of two wound measurement methods in a multi-center, controlled study. *Ostomy Wound Manage* 1994;40:44-8.
- 17 Taylor R. "Mouseeyes": an aid to wound measurement using a computer. *J Wound Care* 1997;6:123-6.
- 18 Iglesias CP, Birks Y, Nelson EA, Scanlon E, Cullum NA. Quality of life of people with venous leg ulcers: a comparison of the discriminative and responsive characteristics of two generic and a disease specific instruments. *Qual Life Res* 2005;14:1705-18.
- 19 Dumville J, Worthy G, Soares M, Bland JM, Cullum M, Dowson C, et al. VenUS II: a randomised controlled trial of larval therapy in the management of leg ulcers. *Health Technol Assess* 2009;13:1-182.
- 20 Margolis DJ, Berlin JA, Strom BL. Which venous leg ulcers will heal with limb compression bandages? *Am J Med* 2000;109:15-9.
- 21 Collett D. Modelling survival data in medical research. 2nd ed. Chapman & Hall/CRC Press, 2003.
- 22 Agresti, A. *Categorical data analysis*. Wiley, 2002.
- 23 Cullum N, Nelson EA, Flemming K, Sheldon T. Systematic reviews of wound care management: (5) beds; (6) compression; (7) laser therapy, therapeutic ultrasound, electrotherapy and electromagnetic therapy. *Health Technol Assess* 2001;5:1-221.
- 24 Cullum NA, Al-Kurdi D, Bell-Syer SEM. Therapeutic ultrasound for venous leg ulcers. *Cochrane Database Syst Rev* 2010;6:CD001180.
- 25 Akbari Sari A, Flemming K, Cullum NA, Wollina U. Therapeutic ultrasound for pressure ulcers. *Cochrane Database Syst Rev* 2006;3:CD001275.
- 26 Busse JW, Kaur J, Mollon B, Bhandari M, Tornetta P 3rd, Schünemann HJ, et al. Low intensity pulsed ultrasonography for fractures: systematic review of randomised controlled trials. *BMJ* 2009;338:b351.
- 27 Altman DG, Schulz KF, Moher D, Egger M, Davidoff F, Elbourne D, et al. The revised CONSORT statement for reporting randomized trials: explanation and elaboration. *Ann Intern Med* 2001;134:663-94.
- 28 The National Archives. Medicines for human use (clinical trials) regulations. 2004. www.uk-legislation.hmso.gov.uk/si/si2004/20041031.htm.

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