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[Intervention Review]

Therapeutic ultrasound for venous leg ulcers

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ABSTRACT

Background

Venous leg ulcers pose a significant burden for patients and healthcare systems. Ultrasound (US) may be a useful treatment for these ulcers.

Objectives

To determine whether US increases the healing of venous leg ulcers.

Search methods

We searched the Cochrane Wounds Group Specialised Register (searched 24 February 2010); The Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* Issue 1, 2010); Ovid MEDLINE (1950 to February Week 2 2010); In-Process & Other Non-Indexed Citations (searched 24 February 2010); Ovid EMBASE 1980 to 2010 Week 07; EBSCO CINAHL 1982 to 24 February 2010.

Selection criteria

Randomised controlled trials (RCTs) comparing US with no US.

Data collection and analysis

Two authors independently assessed the search results and selected eligible studies. Details from included studies were summarised using a data extraction sheet, and double-checked. We tried to contact trial authors for missing data.

Main results

Eight trials were included; all had unclear, or high, risks of bias, with differences in duration of follow-up, and US regimens. Six trials evaluated high frequency US and five of these reported healing at 7 - 8 weeks. Significantly more patients healed with US than without it at 7 - 8 weeks (pooled RR 1.4, 95% CI 1.0 to 1.96), but later assessments at 12 weeks showed the increased risk of healing with US was no longer statistically significant (pooled RR 1.47, 95% CI 0.99 to 2.20). One poor-quality study of high-frequency US found no evidence of an effect on healing after three weeks' treatment.

Two trials evaluated low frequency US and reported healing at different time points. Both trials reported no evidence of a difference in the proportion of ulcers healed with US compared with no US: both were significantly underpowered.

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Authors' conclusions

The trials evaluating US for venous leg ulcers are small, poor-quality and heterogeneous. There is no reliable evidence that US hastens healing of venous ulcers. There is a small amount of weak evidence of increased healing with US, but this requires confirmation in larger, high-quality RCTs. There is no evidence of a benefit associated with low frequency US.

PLAIN LANGUAGE SUMMARY

Ultrasound therapy used for healing venous (varicose) leg ulcers and to improve symptoms

Venous leg ulcers are common, especially in the elderly. They are caused by damage or blockages in the veins of the legs, which in turn lead to pooling of blood and increased pressure in these veins. Eventually, these changes can damage the skin and lead to ulcer formation.

Compression with stockings or bandages is the most widely used, and acceptable, treatment for venous leg ulcers. Ultrasound has been used as an additional intervention, especially for difficult, long-standing ulcers. The mechanisms by which ultrasound waves interact with healing tissues are not fully understood. We conducted a review to establish whether ultrasound speeds the healing and improve symptoms of venous leg ulcers, and examined all the available evidence from medical trials. This showed that there is no strong evidence that ultrasound hastens ulcer healing. There is, however, some weak evidence from poor-quality research that high-frequency ultrasound may increase the healing of venous leg ulcers. This finding, however, requires confirmation in larger and rigorously conducted medical trials before we can be certain that it is true and can be trusted. There is no evidence that low frequency ultrasound improves the healing of venous leg ulcers.

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SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

High frequency US compared to no ultrasound for venous leg ulcers

Patient or population: patients with venous leg ulcers
Settings:
Intervention: High frequency US
Comparison: no ultrasound

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	no ultrasound	High frequency US				
Proportion of ulcers completely healed at 12 weeks - High-frequency US (losses as failures) clinical judgement	**Study population**[1]		**RR 1.47** (0.99 to 2.2)	152 (2 studies)	⊕◯◯◯ **very low**[2,3]	
	32 per 100	**47 per 100** (32 to 71)				
	Medium risk population[1]					
	33 per 100	**49 per 100** (33 to 73)				
	High risk population[1]					
	50 per 100	**74 per 100** (50 to 100)				
Proportion ulcers completely healed at 7 or 8 weeks - Losses as failures	**Study population**		**RR 1.4** (1 to 1.96)	341 (5 studies)	⊕◯◯◯ **very low**[4,5]	
	24 per 100	**34 per 100** (24 to 47)				
	Medium risk population					

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	22 per 100	**32 per 100** (22 to 44)				
HRQoL - not reported	See comment	See comment	Not estimable	-	See comment	Venous leg ulcers adversely affect quality of life however no study measured (or reported) this
Pain - not reported	See comment	See comment	Not estimable	-	See comment	Venous leg ulcers can be extremely painful however no study measured pain in a valid, reliable way

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] High risk of healing at 12 weeks of 50% taken from a large, well conducted RCT where patients all received best practice care (Iglesias et al). Low risk taken from lowest control group healing rate in these trials.
[2] Both studies at unclear or high risk of bias.
[3] Only 60 participants across the two trials reached the endpoint (complete healing).
[4] All studies at high or unclear risk of bias. Only one study described concealed allocation (Callam) and none used blinded assessment of the point at which healing occurred.
[5] Studies were small with a total of only 98 participants reaching the endpoint

BACKGROUND

Description of the condition

The prevalence of active venous leg ulceration has been estimated at 1.5/1000 (Callam 1986), it is higher among women and increases with age (Callam 1985; Margolis 2002). The incidence of venous ulceration in the elderly population has been estimated at 0.76/100 person-year for men, and 1.42/100 person-year for women (Margolis 2002).

Venous disease, including ulceration, constitutes a considerable economic burden, accounting for 2% to 3% of healthcare budget expenditure (Lafuma 1994; Ruckley 1997). Ulcer management is costly (Bosanquet 1992) due to its chronic, recurring nature (Callam 1986) and the need for frequent changes of dressing, home visits, and hospitalisation (Olin 1999). Younger people of working age also experience venous leg ulcers (Nelzen 1994), and their reduced ability to participate in the labour market adds to the economic impact of this disease (Lafuma 1994; Ruckley 1997).

Venous insufficiency is a term used to describe the lack of flow (stasis) of venous blood in the lower limbs. The stasis and pooling of blood in the venous system can be caused by dysfunctional valves of the superficial or deep venous system, deep venous outflow obstruction, or failure of the muscular pump mechanism of the lower limbs (Valencia 2001). The exact pathophysiology behind skin damage and ulcer formation in venous insufficiency is not known; multiple hypotheses include white cell trapping, growth factor trapping, pericapillary fibrin cuffs and fibrinolytic abnormalities (Valencia 2001).

Description of the intervention

The role of therapeutic ultrasound (US) has been explored in a diverse array of conditions including osteoarthritis (Robinson 2001), rheumatoid arthritis (Casimiro 2002), ankle sprains (Van der Windt 2002), pelvic and perineal pain (Hay-Smith 1998), fractures (Busse 2009) and pressure ulcers (Akbari Sari 2006). Therapeutic US has been proposed as a solution for venous leg ulcers that are difficult to treat, and a systematic review is required in order to summarise the results of existing studies accurately.

A typical therapeutic US device consists of a generator that is linked to an applicator head; this enables delivery of multiple frequencies in either a continuous, or pulsed, manner. US is either administered by direct application of the applicator head to the skin, usually with a coupling agent (direct US) (Hart 1998), or indirectly, where the affected area is placed in a constant-temperature water bath and the US administered through the water. Directly-applied US is usually applied to the skin around the ulcer (periulcer skin) rather than directly to the ulcer. Most trials used a pulsed US, with a frequency range of 1 to 3 MHz, and intensity of 0.5 to 1 W/cm², for a duration of 5 to 10 minutes, although there does not seem to be any evidence base for this particular regimen (Hart 1998).

How the intervention might work

The effects of therapeutic US are classified as either thermal or non-thermal on the basis of the proposed physiological effects (Baker 2001; Dyson 1987; Johns 2002; Ter Haar 1999).

Thermal effects

The thermal effects of US are achieved by using a higher intensity application to achieve, and maintain, a rise in tissue temperature to around 40°C (Dyson 1987). Thermal effects have been hypothesized as being capable of increasing blood flow (Dyson 1987), although some trials concluded that there was no obvious effect (Hansen 1973; Hogan 1982; Paul 1955). It has also been suggested that the thermal effects of US produce favourable changes in the physical attributes of collagen-rich structures (Dyson 1987; Ter Haar 1999), although results of research vary in this regard (Enwemka 1990; Larsen 2005).

Non-thermal effects

The non-thermal effects of US are thought to be due to two US-induced phenomena:

1) acoustic streaming: flow and displacement of particles in a fluid medium due to the physical forces of sound waves (Baker 2001; Johns 2002; Ter Haar 1999). Streaming can be further classified into bulk streaming or microstreaming, the latter being more mechanically powerful.

2) cavitation: the formation and behaviour of microenvironmental gases within a fluid medium under the influence of sound waves (Baker 2001; Johns 2002; Ter Haar 1999).

Multiple in vitro studies investigating the non-thermal effect of therapeutic US on the different elements of tissue healing have been conducted. US has been reported as: potentiating enzymatic fibrinolysis (Francis 1992; Olsson 1994); stimulating protein synthesis (Doan 1999; Ross 1983; Webster 1978); inducing an increase in cell proliferation (Doan 1999); inducing release of preformed substances from cells (Ito 2000; Young 1990a); stimulating inflammatory cells (Maxwell 1994; Young 1990a); increasing deposition of collagen (Byl 1992); and promoting formation of new blood vessels (angiogenesis) (Young 1990b). It is not clear, however, whether these effects can be reproduced in vivo, and while some argue that the biophysical phenomena (cavitation and acoustic streaming) do not occur in vivo (Baker 2001), there are conflicting results from different studies (Carstensen 2000; Ter Haar 1981). Furthermore, another study encountered extreme difficulty in observing the occurrence of these phenomena reliably (Crum 1992). Further analysis and discussion of this issue was felt to be out of the scope of this review, but additional helpful

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information can be found in the following reviews (Baker 2001; Johns 2002).

Why it is important to do this review

The effectiveness of US in enhancing the healing of tissue both in vivo and in vitro is uncertain. A Cochrane review of US for treating pressure ulcers concluded that there was no evidence of significant benefit (Akbari Sari 2006). The delivery of US requires investment of health resources and patient time, whilst the equipment can be a potential vector for hospital-acquired (nosocomial) infection (Schabrun 2006), therefore, we need to establish whether it speeds the healing of venous ulcers. In the face of these uncertainties, an up to date review investigating the possible therapeutic effects of US in venous leg ulcers is important.

OBJECTIVES

The review aimed to determine whether venous leg ulcers treated with US heal more quickly than those not treated with US.

METHODS

Criteria for considering studies for this review

Types of studies

For this update, we have included only randomised controlled trials (RCTs) that evaluated the effectiveness of US therapy on the healing of venous leg ulcers. Previous versions of the review also included quasi-randomised studies but we now deem these to be at high risk of selection bias and potentially misleading.

Types of participants

We included trials involving people of any age, and in any care setting, described as having leg ulcers of venous aetiology. As the method of obtaining a differential diagnosis of the ulcer varies, we used study authors' definitions of what constituted a venous leg ulcer.

Trials that recruited people with arterial, diabetic or rheumatoid ulceration were only included if the results for patients with venous ulcers were presented separately.

Types of interventions

The primary intervention was US. Eligible comparison interventions were "no US" in the form of usual care, sham US, or a combination of the two.

Types of outcome measures

Primary outcomes

We sought RCTs which reported objective measures of healing such as time to ulcer healing; proportion of ulcers healed within a specified time period; percentage decrease in ulcer surface area; rate of decrease in ulcer surface area.

Secondary outcomes

1. Health related quality of life.
2. Symptoms e.g. pain, itchiness etc.
3. Costs.
4. Adverse events e.g. pain.

Search methods for identification of studies

Search strategy for the original review and first update can be found in Appendix 1 and Appendix 2 respectively.

Electronic searches

For this second update, we searched the following databases:

- Cochrane Wounds Group Specialised Register (searched 24 February 2010);
- The Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2010, Issue 1);
- Ovid MEDLINE (1950 to February Week 2 2010);
- Ovid MEDLINE In-Process & Other Non-Indexed Citations (Searched 24 February 2010);
- Ovid EMBASE (1980 to 2010 Week 07);
- EBSCO CINAHL (1982 to 24 February 2010).

We searched The Cochrane Central Register of Controlled Trials (CENTRAL) using the following strategy:
#1 MeSH descriptor Varicose Ulcer explode all trees
#2 MeSH descriptor Leg Ulcer explode all trees
#3 (varicose NEXT ulcer*) or (venous NEXT ulcer*) or (leg NEXT ulcer*) or (foot NEXT ulcer*) or (stasis NEXT ulcer*)
#4 (#1 OR #2 OR #3)
#5 MeSH descriptor Ultrasonic Therapy explode all trees
#6 ultrasound NEAR/5 therap*
#7 ultrason* NEAR/5 therap*
#8 (#5 OR #6 OR #7)
#9 (#4 AND #8)
The search strategies for Ovid MEDLINE, Ovid EMBASE and EBSCO CINAHL can be found in Appendix 3, Appendix 4 and Appendix 5 respectively. The Ovid MEDLINE search was combined with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision); Ovid format (Lefebvre 2009). The EMBASE and CINAHL searches were combined with

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the trial filters developed by the Scottish Intercollegiate Guidelines Network (SIGN 2009). There was no restriction by language, date or publication status.

Searching other resources

We attempted to contact researchers to obtain any unpublished data when needed. Reference lists of potentially useful articles were also searched.

Data collection and analysis

Selection of studies

For the initial version of the review, titles and abstracts of studies identified by searches were assessed for eligibility by one review author (KF). Full reports were obtained if, from this initial assessment, they appeared to satisfy the inclusion criteria. Those rejected were checked by another review author (NC). Full papers were checked to identify those that were eligible for inclusion. This was repeated independently by another review author (NC) to provide verification. Any disagreement was resolved by discussion, and, if necessary, by referral to a third review author for adjudication. Details of the studies were extracted and summarised using a data extraction sheet. If data were missing from reports, then attempts were made to contact the study authors to obtain missing information. Studies that were published in duplicate were included only once. Data extraction was undertaken by one review author and checked for accuracy by a second review author.

The same process was followed with different review authors for the subsequent review updates, always with at least two review authors working independently.

Data extraction and management

For this update, all original data were re-extracted by NC and checked by a second review author (SBS).

The following data were extracted:

- country of origin and health care setting;
- eligibility criteria: baseline patient characteristics by treatment group;
- details of the US regimen received by the intervention group plus co-interventions;
- details of the ulcer care regimen received by the comparison group;
- primary and secondary trial outcome(s);
- results including primary and secondary outcomes, adverse events, numbers of withdrawals, all by treatment group.

Assessment of risk of bias in included studies

For the update of this review, two review authors independently assessed each included study, without blinding to journal or authorship, using the Cochrane Collaboration tool for assessing risk of bias (Higgins 2009). This tool addresses six specific domains, namely sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other issues (e.g. extreme baseline imbalance) (see Appendix 6 for details of criteria on which the judgements were based). Blinding and completeness of outcome data were assessed for each outcome separately. We completed a risk of bias table for each eligible study. We discussed any disagreement amongst all review authors to achieve a consensus.

We presented an assessment of risk of bias using a risk of bias summary figure (Figure 1), which presents all of the judgments in a cross-tabulation of study by entry. This display of internal validity indicates the weight the reader may give the results of each study. Studies were classed as being at high risk of bias if any one of the criteria received a "No" classification.

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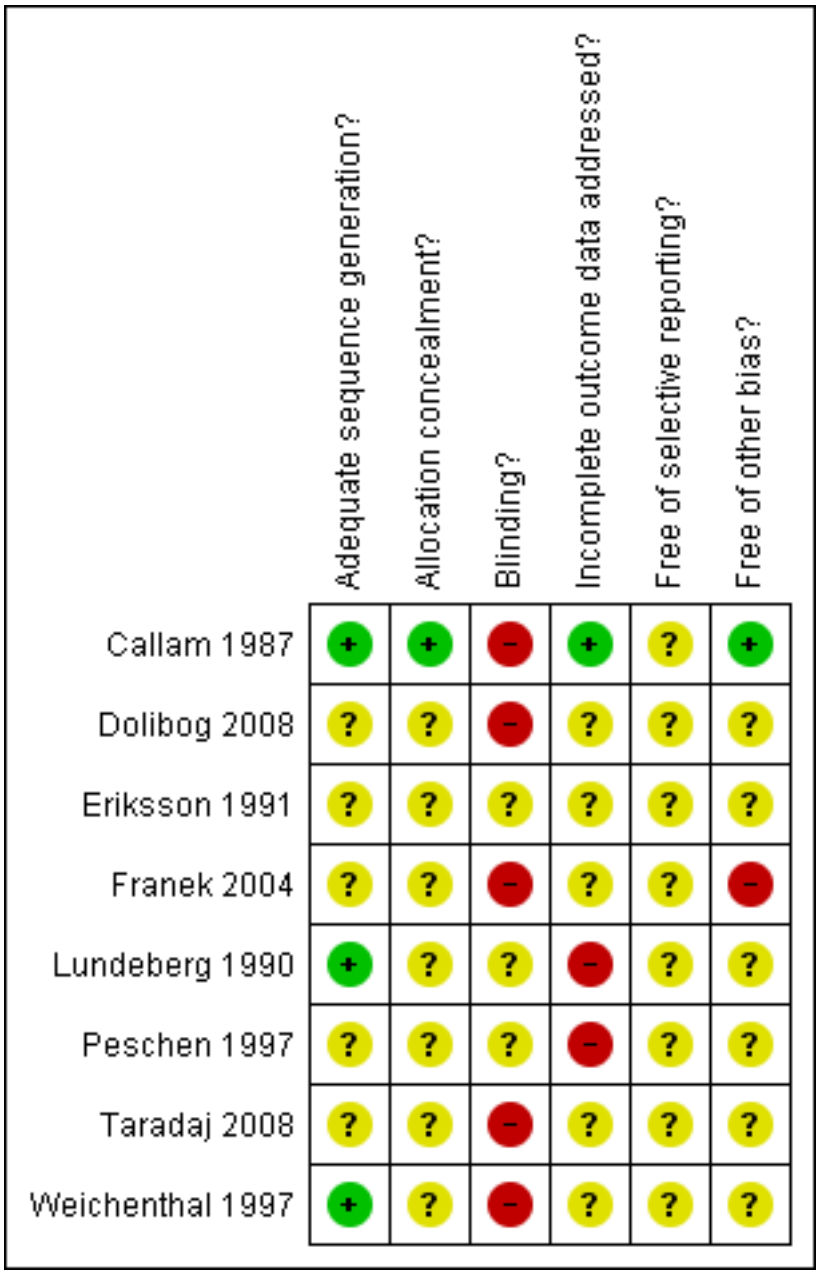
Figure 1. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



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Dealing with missing data

High rates of withdrawal from trials are common in chronic wounds research, and trialists have tended to deal with such patients as being lost-to-follow-up and ignored them in the analysis. This approach clearly disrupts randomisation, and has a high potential for introducing bias - largely by ignoring patients who have failed to heal. For the main analysis we have, therefore, regarded participants who were lost-to-follow-up (i.e. randomised but not appearing in the analysis) as unhealed - where healing was the main endpoint - as this seems the most plausible outcome, however, we have also tested this approach by conducting complete case analyses alongside (see Analysis 2.3; Analysis 2.4). Application and comparison of both these approaches was not pre-specified in the original protocol.

Assessment of heterogeneity

Heterogeneity was tested for using the Chi² statistic, and the amount of variation due to heterogeneity was assessed using I² (Higgins 2003).

Data synthesis

The studies included in the review were combined by narrative overview with meta-analysis of outcome data where appropriate, conducted using RevMan 5 software. Relative risk with 95% confidence intervals (CI) was calculated for each trial with important dichotomous outcomes (e.g. number of ulcers healed). Continuous data were presented and analysed using differences in means with 95% CI. For this update the evidence was presented according to US frequency (high-frequency being 1MHz and low-frequency being 30kHz). We compiled two Summary of Findings Tables using Gradeprofiler; one each for high frequency and low frequency ultrasound. We estimated control group event rates for patients at medium risk of healing using the average risk of healing in the included studies; we estimated control group event rates for patients at high risk of healing from a large, well conducted trial that exposed participants to best practice (Iglesias 2004).

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification; Characteristics of ongoing studies.

The initial version of this review included seven studies. The first update included the original seven plus one new study (Franek 2004), making a total of eight (Callam 1987; Dyson 1976; Eriksson 1991; Franek 2004; Lundeberg 1990; Peschen 1997; Roche 1984; Weichenthal 1997). For this second update we have included two new RCTs (Dolibog 2008; Taradaj 2008), but excluded two previously included studies on the grounds that they used quasi random allocation methods and were consequently at substantial risk of selection bias (Dyson 1976; Roche 1984). A total of six studies were therefore excluded from the review at the full text stage as they were not randomised controlled trials (Dissemond 2003; Dyson 1976; Kavros 2007b; Roche 1984; Tan 2007) or involved people with arterial rather than venous ulcers (Kavros 2007a). We identified a further two citations to potentially eligible studies which require translation and are therefore classified as awaiting assessment (Franek 2006; Taradaj 2007) and one study which is ongoing and expected to report late in 2010 (Nelson 2006). This update, therefore, includes a total of eight RCTs. Most of the included studies were small; sample sizes ranged between 24 and 108. All patients were diagnosed with venous leg ulceration, and five trials out of eight reported the criteria by which this diagnosis was made (Dolibog 2008; Eriksson 1991; Peschen 1997; Taradaj 2008; Weichenthal 1997).

Therapeutic US was compared with sham or placebo US in three trials (Eriksson 1991; Lundeberg 1990; Peschen 1997), and in the remaining five it was compared with standard ulcer care. Three trials evaluated directly-applied US (Callam 1987; Eriksson 1991; Lundeberg 1990), and the other five evaluated US that was indirectly-applied to the ulcers though water. Six trials evaluated high-frequency therapeutic US (Callam 1987; Dolibog 2008; Eriksson 1991; Franek 2004; Lundeberg 1990; Taradaj 2008), whilst the other two evaluated low-frequency US (Peschen 1997; Weichenthal 1997).

High frequency ultrasound

Lundeberg 1990 randomised 44 patients with venous leg ulcers to receive US directly to the ulcer surface and surrounding tissue (pulsed 1 MHz , 0.5 W/cm² for 10 minutes) plus standard treatment, or placebo (sham) US plus standard treatment. After withdrawals, 32 participants remained: 17 in the US group and 15 in the placebo group. The regimen of standard treatment consisted of cleansing with saline, application of paste, support bandages and an exercise program. The frequency of treatment varied over the course of the 12-week study, decreasing from three times weekly for the first four weeks to twice weekly for the subsequent four weeks, and then once weekly for the final four weeks. The objective outcome was the number of ulcers healed, and the percentage of initial ulcer area present after 4, 8 and 12 weeks.

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In a similar study, Eriksson 1991 compared an US regimen of 1 MHz, 1.0 W/cm² US for 10 minutes, twice weekly for eight weeks with sham US. All participants received standard treatment, consisting of paste-impregnated bandage and a self-adhesive elastic bandage. The 38 participants were people referred from secondary and primary health care settings; ulcer aetiology was confirmed by means of a clinical examination and patient questionnaire. People with an allergy to standard treatment, arterial disease, rheumatoid arthritis, or with diabetic or traumatic ulcers were excluded from this study. The outcomes measured were the number of ulcers healed, and the percentage of initial ulcer area present at two-week intervals for eight weeks.

Callam 1987 randomised 108 patients attending a physiotherapy clinic for treatment of chronic venous ulcers to receive either US (pulsed 1 MHz, 0.5 W/cm², 1 minute per probe head) and standard treatment, or standard treatment alone. Standard treatment consisted of cleansing with 1% cetrimide/normal saline, application of *Arachis* oil to the surrounding skin, Calaband paste bandage and Lestreflex support bandage, plus standardised exercise. Ulcer aetiology was assessed on basis of a questionnaire and clinical examination, participants were excluded if they were allergic to treatment or demonstrated arterial disease. Treatment occurred weekly for 12 weeks. Healing was measured in terms of percentage decrease in ulcer area, and the number of ulcers completely healed under 12 weeks.

Franek 2004 randomised 65 people between three treatment groups; two received different intensities of pulsed, 1 MHz US (either 0.5 or 1 W/cm²) in a water bath with a temperature of 34°C plus standard treatment of topical agents, while the third group received standard treatment only. Standard treatment comprised potassium permanganate baths, wet dressings of 0.1 copper sulphate solution, fibrolan compresses, chloramphenicol, colistin, gentamicin and a single layer of compression bandage. Patients with arterial disease and diabetes were excluded. All three groups were admitted to hospital for three weeks, which was also the total duration of follow up. Importantly, apart from the differences in local wound treatment (above), the intervention groups were treated in a university hospital, and the control group in another nearby hospital resulting in a high risk of performance bias. Treatment sessions occurred daily, and lasted from 5 to 10 minutes. Degree of healing was quantified by the weekly rate of decrease in ulcer surface area, volume and the number of ulcers completely healed.

Dolibog 2008 randomised 70 people who had previously received venous surgery between two trials arms, one of which received 0.5W/cm² pulsed US at 1 MHz frequency using the indirect, water bath method (see above). Treatment continued on six days out of every seven, for seven weeks. Co-interventions included compression hosiery, saline soaked gauze to the ulcers and 1 g flavonoid fraction daily. The control group received the compression stockings, flavonoid fraction and saline soaks. The outcomes measured were the number of ulcers completely healed, and extensive dimensional measurements of the ulcers, including mean ulcer area.

Taradaj 2008 conducted a four-group randomised trial with 81 participants. Groups 1 and 2 agreed to, and received, venous surgery which included crossectomy, partial stripping of the greater or lesser saphenous vein, local phlebectomy and ligation of insufficient perforators, as applicable to each patient. Participants in Groups 3 and 4 had refused surgery. Group 1 and 3 were randomised to receive US therapy, using the indirect, water bath approach, at 0.5W/cm² at 1MHz, plus compression therapy, saline-soaked gauze to the ulcer and 1 g of flavonoid fraction daily. Groups 2 and 4 received compression therapy, saline soaks and flavonoid. US was received on six days out of every seven for seven weeks. The outcomes measured included the number of ulcers completely healed, plus extensive dimensional measurements of the ulcers, including volume and area.

Low frequency ultrasound

Peschen 1997 placed participants' legs in a 32° to 34 °C water footbath and applied continuous 30 KHz, 0.1 W/cm² US that was compared with sham US procedure. Both treatment groups also received standard treatment of hydrocolloid dressing plus compression bandaging. The trial randomised 24 people attending an outpatient clinic, each with a venous ulcer larger than 2 cm² of at least three months' duration. Venous aetiology was confirmed by means of history, Doppler sonography and light-reflection-rheography. People with gastrointestinal, liver, cardiac, or renal disease, diabetes, polyneuropathy, rheumatoid arthritis, malignancy, or allergy to standard treatment were excluded. Treatment sessions lasted 10 minutes and took place three times a week for 12 weeks. The outcomes measured were number of ulcers completely healed at 12 weeks and percentage reduction in ulcer area at the end of the treatment and after 25 weeks.

Weichenthal 1997 employed the same indirect US regimen as Peschen 1997. Thirty-seven people were randomised to receive either 30 kHz of US at 0.1 W/cm² for 10 minutes from an US applicator mounted in a footbath, plus conventional treatment, or conventional treatment alone, which consisted of fibrinolytic agents, antibiotics, antiseptic agents, and occlusive dressings. Participants each had a venous ulcer of more than three months' duration, and no evidence of arterial disease or diabetes. Follow-up was for eight weeks, with outcome measures of number of ulcers completely healed and percentage decrease in ulcer area.

Risk of bias in included studies

We classified studies as being at high risk of bias if they were rated "No" for any of the four key criteria (randomisation sequence generation, allocation concealment, blinding and incomplete outcome data addressed). Every study was deemed to be at high risk of bias, except Eriksson 1991, which was rated unclear for every criterion (see Figure 2; Figure 1 for a summary of the risk of bias).

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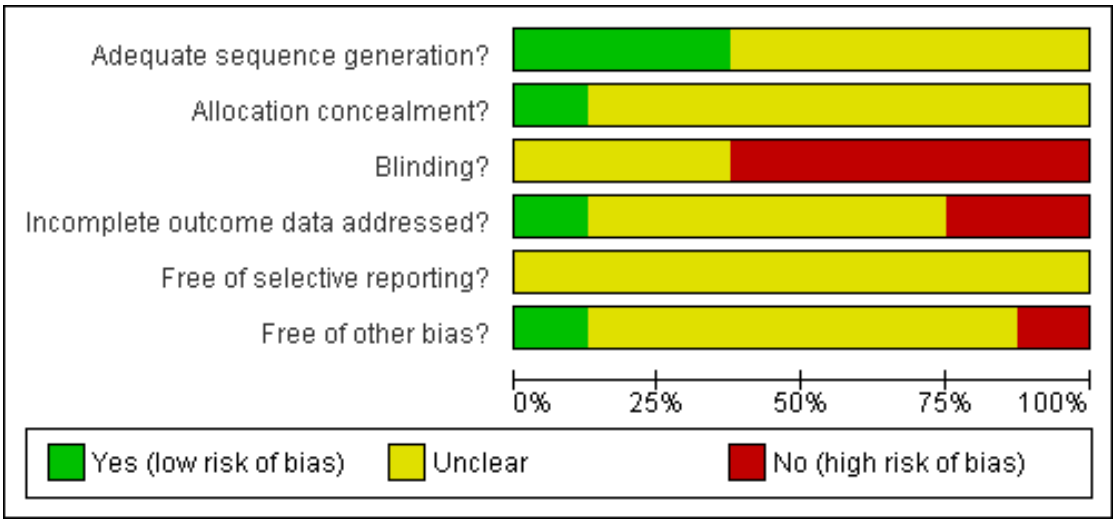
Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.



Adequacy of randomisation process

All study authors stated that the participants were randomised. Three studies provided sufficient information to indicate that participants were randomised according to an adequate randomisation sequence. Weichenthal 1997 used computer-generated random numbers, Lundeberg 1990 and Callam 1987 used randomised permuted blocks. The randomisation method was not mentioned in five studies (Dolibog 2008; Eriksson 1991; Franek 2004; Peschen 1997; Taradaj 2008).

Allocation concealment

Callam 1987 used a central office to conceal allocation and was the only included study to describe concealed allocation adequately. Every other study was rated unclear for allocation concealment.

Blinding

No study reported what could be regarded as fully-blinded outcome assessment. In three studies (Callam 1987; Eriksson 1991; Lundeberg 1990), ulcer tracings were completed by unblinded staff but the analysis (computer-aided measurement of ulcer area) of coded tracings was undertaken by staff who were blinded to treatment group. Whilst this probably affords some protection against measurement bias, the accuracy of initial tracings may have been adversely influenced by the awareness of the tracer of the allocation group. Two trials did not provide sufficient information for us to judge whether outcome assessment was blinded (Dolibog 2008; Peschen 1997). Three trials clearly did not employ any blinding of outcome assessment (Franek 2004; Taradaj 2008; Weichenthal 1997). Since the judgement of when healing actually occurs is, to a certain extent, subjective, we classified trials without blinded outcome assessment as being at high risk of bias even if this was the only criterion failure, as in the case of Callam 1987.

Incomplete outcome data

The only trial that explicitly attempted to reduce the bias associated with incomplete outcome data was Callam 1987; five trials were unclear (Dolibog 2008; Eriksson 1991; Franek 2004; Taradaj 2008; Weichenthal 1997), and the remaining two appeared to have omitted non-compliant patients from their analyses, thereby introducing a high risk of bias (Lundeberg 1990; Peschen 1997).

Other biases

The results of Franek 2004 should be viewed with extreme caution as the treatment groups differed in important aspects of care apart from the US treatment. The non-US group received an intensive wound treatment regimen that was not given to the two US groups, and, furthermore, while the patients in the two US groups were admitted to the same hospital, the non-US group were admitted to a completely different hospital.

Outcome measures used

There is a great deal of variation in wound healing trials in the selection, as well as reporting of outcome measures, and very little methodological research to validate the wound outcome measures used. Arguably, time to wound healing is the most patient-oriented

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outcome, since, even in trials of treatments for chronic wounds, the majority do achieve healing. Survival analysis is the most appropriate strategy for analysing a time-to-event outcome such as time-to-healing, with hazard ratio as the effect measure, however, this is very rarely used. Three trials (Callam 1987; Lundeberg 1990; Peschen 1997) used life table methods to compare healing rates but did not report hazard ratios. All trials did report the proportion of ulcers completely healed at arbitrary and varying follow-up times (duration of follow-up ranged between three weeks (Franek 2004) and 12 weeks (Callam 1987; Lundeberg 1990; Peschen 1997). The remaining trials reported healing by seven or eight weeks.

None of the included trials appears to have measured the secondary outcomes of health-related quality of life, adverse events or costs in a systematic way (certainly did not report them). Several trials reported numbers of withdrawals due to pain or bleeding, and mentioned some adverse events; these have been described in narrative form alongside the trial results.

Effects of interventions

See: **Summary of findings for the main comparison** High frequency US compared to no ultrasound for venous leg ulcers; **Summary of findings 2** Low frequency US compared to no ultrasound for venous leg ulcers

For this update the results are presented separately for high and low frequency US, though this approach was not pre-specified in the protocol. We present the (unpooled) results of all six trials that reported ulcer healing data at seven or eight weeks in Analysis 1.1. Five out of the six trials reported more healing in the US-treated groups compared with no US, although in only one of these trials was the difference statistically significant (Callam 1987).

Three RCTs evaluated directly-applied US (all high-frequency) (Callam 1987; Eriksson 1991; Lundeberg 1990) and five RCTs evaluated indirectly-applied US: i.e. Dolibog 2008; Franek 2004; and Taradaj 2007 (all high-frequency) and Peschen 1997 and Weichenthal 1997 (low-frequency US delivered via a waterbath). We regarded indirectly- and directly-applied US as sufficiently similar to be analysed together. Three trials compared US therapy with sham US (Eriksson 1991; Lundeberg 1990; Peschen 1997), whilst five compared US therapy with standard treatment (Callam 1987; Dolibog 2008; Franek 2004; Taradaj 2007; Weichenthal 1997).

There was much heterogeneity in the nature and timing of outcomes reported across all trials. Trialists reported a combination of the number of ulcers healed at specified (and varied) time points, mean change in ulcer size at varied time points, or both.

High frequency ultrasound

Six RCTs evaluated high-frequency US involving a total of 406 randomised participants (Callam 1987; Eriksson 1991; Lundeberg 1990; Dolibog 2008; Taradaj 2008; Franek 2004). The trial by Franek 2004 reported numbers of ulcers healed, mean and median change in ulcer area at 3 weeks only. Taradaj 2008 and Dolibog 2008 reported healing at 7 weeks whilst the trials by Eriksson 1991; Callam 1987 and Lundeberg 1990 reported healing at eight weeks. Callam 1987 and Lundeberg 1990 also reported ulcers healed at 12 weeks. We pooled the results of these six RCTs for the outcome of complete ulcer healing at any time point (I^2=0) using a random effects model. There was no statistically significant difference in the relative risk of healing between US treated patients and those not receiving US (RR 1.34, 95% CI 0.99 to 1.80) (Analysis 2.1).

Ulcers healed at 3 weeks

One trial (Franek 2004) reported outcomes at three weeks only; this is an extremely short duration of follow up, during which one would expect to see very few ulcers completely healing.

The results of Franek 2004 should be viewed with extreme caution for several reasons; apart from the paucity of endpoint data due to the brief follow up the trial was confounded and likely to be subject to important performance bias - we have included it here since we did not pre-specify that we would exclude trials where US was not the only systematic difference in treatments. The trial involved three treatment arms: two US arms (1 W/cm² and 0.5 W/cm²) and a control arm with no US. However, the control group received co-interventions (in the form of local wound treatments) that were not received by the US patients (potassium permanganate and wet dressings of 0.1 copper sulphate solution plus compresses of fibrolan, chloramphenicol, colistin, gentamicin), and, furthermore, they were treated in a different hospital. At three weeks complete healing had occurred in 1/22 (4.5%) of the group receiving 1 W/cm² US, 3/21 (14.3%) of the group receiving 0.5 W/cm² US, and 1/22 (4.5%) of people receiving no US. For the purposes of the main analysis we have pooled both US arms and compared them with no US. This preserves randomisation but results in unequally sized groups. There was no statistically significant difference in the proportion of ulcers healed with US compared with no US at three weeks (RR 2.05, 95% CI 0.24 to 17.23) (Analysis 2.2).

There was no reporting of secondary outcomes (health-related quality of life (HRQoL), pain, adverse events or costs) in this trial.

Healing at 7 - 8 weeks

Callam 1987: there was a statistically significant increase in the risk of healing associated with US over standard therapy alone at eight weeks (eight week data read from the graph in the published paper). Twenty-three out of 52 participants randomised to US healed by eight weeks (44%), compared with 14 out of 56 (25%) randomised to standard treatment alone. The relative risk (RR) for healing with US compared with no US was 1.77, 95% CI 1.02 to 3.06 (Analysis 1.1).

Eriksson 1991: there was no statistically significant difference in outcomes between US and sham at 8 weeks. The ulcers of 6/19 participants (32%) randomised to the US group had healed

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by eight weeks compared with 4/19 (21%) in the sham group (RR 1.50, 95% CI 0.50 to 4.48) (Analysis 1.1). Thirteen out of 38 participants randomised (34%) withdrew from this trial. The mean percentage of initial ulcer area remaining at 8 weeks was 42% (SD 9%) in the US group and 48% (SD 13%) in the sham group (no statistically significant difference).

Lundeberg 1990: there was no statistically significant difference between ultrasound and sham ultrasound in the proportion of participants whose ulcers healed completely. At eight weeks 5/22 (23%) participants healed with US compared with 3/22 (14%) in the sham group (RR 1.67, 95% CI 0.45 to 6.14 (Analysis 1.1). The mean percentage of initial ulcer area remaining at 8 weeks was 47% (SD 8%) in the US group compared with 53% (SD 10%) in the sham group.

Taradaj 2008: for the purposes of the main analysis we pooled the results for both US arms (surgery plus no surgery) and both control arms (surgery plus no surgery). At seven weeks there was no statistically significant difference in the proportion of ulcers healed between those receiving US and those who did not (RR 1.30, 95% CI 0.62 to 2.74) (Analysis 1.1). The mean reduction in ulcer area at 7 weeks was also reported but without variance data so could not be plotted here. The authors reported mean reduction in ulcer area in the surgical patients of 58.21% with US compared with 58.36% (no US); and for the non-surgery patients the reduction was 56.67% with US and 36.09% without US.

Dolibog 2008: at seven weeks 10 out of 33 participants in the US had completely healed compared with 12 out of 37 in the control group (no statistically significant difference, RR 0.93, 95% CI 0.47 to 1.87) (Analysis 1.1). Dolibog 2008 also reported the mean wound area at baseline and 7 weeks. Mean ulcer area at baseline in the US group was 24.27cm^2 (SD 17.12) which reduced to 13.15cm^2 (SD 11.55). Mean baseline area in the control group was 24.92cm^2 (SD 16.19) which reduced to 13.12cm^2 (SD 14.57) (no evidence of a difference).

We regarded it as appropriate to pool the results for Callam 1987; Eriksson 1991; Lundeberg 1990; Taradaj 2008 and Dolibog 2008 for seven to eight weeks' follow-up as there appeared to be no statistical heterogeneity (I^2=0). We regarded those randomised but lost to follow up as unhealed in this analysis (i.e., they appeared in the denominator). After seven to eight weeks of US treatment, there was a statistically significant increase in the proportion of ulcers healed with US compared with no US (pooled RR 1.40, 95% CI 1.00 to 1.96; I^2=0, fixed-effect) (Analysis 2.3). When this analysis is undertaken using a random effects model (possibly the more appropriate approach given the differences between the trials), this difference is no longer statistically significant (RR 1.4, 95% CI 0.99 to 1.96, not shown). Similarly this difference is no longer statistically significant (RR 1.36, 95% CI 0.98 to 1.88 Analysis 2.3) when a complete case analysis is undertaken.

Healing at 12 weeks

Callam 1987 also reported healing after 12 weeks of treatment at which point there was no statistically significant difference between US plus standard care and standard care alone (RR 1.58, 95% CI 0.97 to 2.58) (Analysis 2.4). Callam 1987 also reported percentage decrease in ulcer area over time and mean residual ulcer area remaining at 12 weeks as a % of baseline however did not provide any variance data around the mean estimates and this analysis is problematic since 37 participants had healed completely. They reported that at 12 weeks 9% of initial ulcer area remained in the US group compared with 27% in the standard care group and that this difference was statistically significant in favour of US.

At 12 weeks' follow up, Lundeberg 1990 reported that 10/22 (45%) ulcers healed with US compared with 8/22 (36%) in the sham group (RR 1.25, 95% CI 0.61 to 2.56, no statistically significant difference Analysis 2.4). Lundeberg 1990 also reported percentage initial ulcer remaining at 12 weeks (39%, SD 5% with US and 43%, SD 6% with sham US, no statistically significant difference).

Pooling the two studies found no statistically significant difference in the proportions of participants whose ulcers had healed at 12 weeks with US compared with no US (RR 1.47, 95% CI 0.99 to 2.20, fixed effect I^2=0) (Analysis 2.4); however, this comparison is statistically underpowered for detecting a clinically important treatment effect, with only 152 participants randomised. The result did not change when a random effects model was applied. Both trials were regarded as being at high risk of bias for healing outcomes.

Secondary outcomes

In the Callam 1987 trial a total of 26 out of 108 randomised participants withdrew (24%), leaving 76% of those randomised to provide outcome data. Proportions and reasons for withdrawal were similar across the two treatment groups. Eleven out of 52 randomised (21%) withdrew from the US group for reasons of allergy (four), pain (four), death (two), and withdrawn consent (two). Fifteen out of 56 (27%) withdrew from the standard care group for reasons of allergy (six), pain (three), deterioration (two), withdrawal of consent (three), and newly-diagnosed arterial disease (one).

In the Eriksson 1991 trial 7/19 (37%) participants randomised withdrew from the US group (three for "allergy", two for pain, and two withdrew consent) compared with 6/19 (32%) from the control group (two for "allergy", one for pain, three withdrew consent).

In the Lundeberg 1990 trial, 5/22 participants (23%) randomised to US withdrew (two for "allergy", one for pain, two withdrew consent) compared with seven out of 22 (32%) from the sham group (three for "allergy", one for pain, three withdrew consent). Dolibog 2008; Franek 2004 and Taradaj 2008 did not report any withdrawals or adverse events.

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Low-frequency ultrasound

Two RCTs evaluated indirectly-applied, low-frequency US. Both Peschen 1997 and Weichenthal 1997 applied 30 kHz, 0.1 W/cm² three times a week via a water bath. These trials reported healing outcomes at different time points (12 weeks in Peschen 1997 and eight weeks in Weichenthal 1997).

Healing at 8 - 12 weeks

Peschen 1997: there was no statistically significant difference between US and no US in the proportion of participants whose ulcers healed completely over the 12 weeks of the trial (2/12 ulcers healed in the US group compared with 0/12 ulcers in the sham group; RR 5.00, 95% CI 0.27 to 94.34) (Analysis 3.1).

Weichenthal 1997: by eight weeks one ulcer had healed completely in the US group compared with none in the standard therapy group (RR 2.85, 95% CI 0.12 to 65.74) (Analysis 3.1). This difference was not statistically significant.

We pooled these two studies for the outcome of healing at 8 - 12 weeks (I^2=0), using a fixed effect model (Analysis 3.1). There was no statistically significant difference in the risk of healing associated with low frequency US applied twice a week (RR 3.91, 95% CI 0.47 to 32.85). This result did not change appreciably when a random effects model was applied (RR 3.85, 95% CI 0.45 to 32.84, not shown) however as there were only three ulcers healed across these two trials this comparison is underpowered and a treatment effect cannot be excluded.

Secondary outcomes

Weichenthal 1997: Microbleeding around the ulcer occurred in 5/12 ulcers in the US group compared with none in the sham US group. Patients' experiences of pain were reported, however, this does not appear to have been systematically measured. Pain was reported as follows: US group: one patient reported no change in baseline pain, eight patients complained of pain "prior to treatment"; pain was no longer reported by any patients starting in week four. Sham group: one patient reported no change in baseline pain; 10 patients complained of pain at various time points.There was no reporting of HRQoL or costs.

Peschen 1997: treatment-related adverse events were only reported for patients in the US group. Eleven out of 19 patients in the US group felt no pain or mild pain on fewer than three treatment occasions; 7/19 US patients reported pain on more than two occasions, but severe pain on fewer than three treatment occasions; 1/19 US patients reported severe pain on more than two occasions. Twelve out of 19 US patients experienced erythema on more than two occasions. There was no reporting of HRQoL or costs.

Sensitivity analyses

Where the numbers randomised differed from the numbers analysed, we undertook the primary analysis using the numbers randomised as the denominator (i.e. assuming losses to follow-up were unhealed). We then examined the impact of this decision in a sensitivity analysis where we analysed complete cases only.

High-frequency US

Looking at the trials which evaluated high-frequency US and reported outcomes at 7 - 8 weeks (Callam 1987; Eriksson 1991; Lundeberg 1990; Dolibog 2008; Taradaj 2008) (Analysis 2.3), we can see that the result of complete case analysis (RR for healing with US 1.36, 95% CI 0.98 to 1.88) is not substantively different from the result when losses are regarded as unhealed (RR for healing with US 1.4, 95% CI 1.00 to 1.96). At 12 weeks follow up, the RR for healing with US compared with no US using a complete case analysis is 1.35, 95% CI 0.94 to 1.93; whilst when regarding losses as unhealed the RR is 1.47, 95% CI 0.99 to 2.20 (Analysis 2.4).

Low-frequency US

In the trial of Peschen 1997, two participants dropped out of the non-US group for non-compliance; there was no appreciable difference in the result whether complete case analysis was used or whether losses were regarded as unhealed (RR for ulcer healing at 12 weeks for US compared with no US when losses regarded as unhealed is 5.00, 95% CI 0.27 to 94.34; RR for ulcer healing at 12 weeks using complete case analysis is 4.23, 95% CI 0.23 to 79.10, not shown).

Summary of Findings Table

We have included Summary of Findings tables (Summary of findings for the main comparison; Summary of findings 2) in this update, which give a concise overview and synthesis of the volume and quality of the evidence. The Summary of Findings tables (one each for high and low frequency US) confirm our conclusion that the quality of evidence is very low and on balance there is no strong evidence of a benefit of US on venous ulcer healing.

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ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Low frequency US compared to no ultrasound for venous leg ulcers

Patient or population: patients with venous leg ulcers
Settings: any
Intervention: Low frequency US
Comparison: no ultrasound

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	no ultrasound	Low frequency US				
Proportion ulcers completely healed at 8 - 12 weeks	**Study population**[1]		**RR 3.91** (0.47 to 32.85)	61 (2 studies)	⊕◯◯◯ **very low**[2,3]	
	0 per 100	**0 per 100** (0 to 0)				
	High risk population[1]					
	30 per 100	**100 per 100** (14 to 100)				
HRQoL - not reported	See comment	See comment	Not estimable	-	See comment	Venous leg ulcers have a large, negative impact on quality of life however no study reported this
Pain - not reported	See comment	See comment	Not estimable	-	See comment	Venous leg ulcers can be extremely painful and treatments can increase the level of pain or discomfort. No study measured pain using accepted approaches

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] With best practice care (high compression bandaging), a baseline risk of healing at 10 weeks (midpoint of 8 and 12 weeks) would be approximately 30% (Iglesias et al).
[2] Both studies at unclear or high risk of bias.
[3] Only 3 participants in the two trials reached the endpoint (complete ulcer healing). All 3 participants were in the ultrasound arms of the trials.

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DISCUSSION

This systematic review has identified no strong evidence that therapeutic US speeds the healing of venous leg ulcers, however, all the trials included were too small to detect clinically important treatment effects, and even meta-analysis of these small trials will not provide adequate statistical power. Furthermore, most of the evidence was at high risk of bias due to common failings in trial conduct, most notably the lack of blinded outcome assessment and failure to deal with incomplete outcome data appropriately. Poor reporting was also an issue, and in all but one case it was impossible to discern whether the randomisation was adequately concealed.

Whilst there was some evidence that high-frequency (1 MHz) therapeutic US (used as infrequently as once a week) may increase the proportion of ulcers healed at eight weeks, this effect seemed to have disappeared by 12 weeks, and the risk of bias means that this is extremely weak evidence and insufficient to act upon clinically. There was no evidence at all of a treatment effect associated with low frequency US; though again low statistical power and risk of bias means we cannot entirely rule out an effect.

None of the trials identified measured health related quality of life. Perhaps more surprisingly, none appears to have measured pain in a systematic, validated way (e.g. by using a visual analogue scale) nor collected adverse event data systematically - these failings must be reversed in future studies.

Future wounds trials should adhere to the expected international standards of RCTs in other areas of health care. This would include concealed allocation; blinding (or at least blinded adjudication of outcome assessment); more complete ascertainment of endpoints with intention-to-treat analysis. In future trials, where participants are withdrawn from trial treatments, as frequently occurs, they should not be withdrawn from the trial (unless of course they withdraw consent); rather they should be followed-up as planned, and their outcomes analysed by intention-to-treat, since to do otherwise introduces serious bias. Furthermore, ideally, trialists should follow-up participants for at least six months in order to observe healing, and report time to healing as the primary outcome (since this is the outcome that is usually most appropriate and likely to matter the most to patients). More sophisticated methods of survival analysis, such as Cox regression, should then be used.

There have been previous systematic reviews of US for wound healing (e.g. Johannsen 2002), which concluded that whilst the evidence was weak, US appeared to be effective. The Johannsen 2002 review included six trials, two of which were excluded from this review (Roche 1984 and Dyson 1976) as they are not RCTs. We have identified and included four further trials and in doing so, we have weakened the evidence in support of therapeutic US as a treatment for venous ulcers.

In summary, we have found no strong evidence to suggest that therapeutic US increases the healing of venous leg ulcers.

AUTHORS' CONCLUSIONS

Implications for practice

There is no evidence to support the routine use of therapeutic ultrasound (US) as a treatment for venous leg ulcers. The evidence that exists is of low quality and volume, and a beneficial effect cannot be ruled out.

Implications for research

An adequately-powered randomised controlled trial is required to determine whether therapeutic ultrasound (US) does speed the healing of venous ulcers. Such a trial might either be explanatory, and compare US with sham US, or probably more usefully, be pragmatic and attempt to establish whether US is likely to be effective if used in clinical practice. This would probably mean evaluating an US regimen that is feasible, and does not require hospital admission or multiple treatments per week. In a pragmatic trial, the comparisons would be the best available standard treatment plus US, compared with standard treatment alone. Outcomes should include time to ulcer healing, quality of life (including pain), adverse events and costs.

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* *Indicates the major publication for the study*

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CHARACTERISTICS OF STUDIES

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

Callam 1987

Methods	Patients with chronic leg ulcers who were attending physiotherapy departments in Scotland, UK, individually randomised to receive US or standard care
Participants	108 patients attending participating physiotherapy clinics. Exclusion criteria included allergy to standard treatments, peripheral vascular disease. US group: 52; Standard treatment group: 56.
Interventions	US group: once weekly pulsed, direct US 0.5 Watt per cm^2 at a frequency of 1 MHz, applied directly to the tissue surrounding the ulcer for 12 weeks or until healing (whichever occurred first) plus standard treatment (see below). Standard treatment group: standard regimen of 1% cetrimide in normal saline, followed by *Arachis* oil to the skin (no massage), a paste bandage (Calaband), a Lestreflex support bandage and an exercise instruction sheet
Outcomes	The number of ulcers completely healed at 12 weeks (losses considered as treatment failures). The mean % of initial ulcer area remaining at 12 weeks. Withdrawals by treatment group with reasons.
Notes	Ulcers were traced; tracers were not blind to treatment group, but analysis of tracings was blinded. Withdrawn patients were censored at the point of withdrawal except for those who were withdrawn due to deterioration, who were regarded as unhealed at 12 weeks. NB the original Lancet paper report of this trial stated that the US frequency was 1 mHz. We contacted Mr Callam, the Principal Investigator, in November 2009. He confirmed that the frequency was 1 MHz (bringing the trial into line with most of the others). Duration of follow-up: 12 weeks.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	"Patients were randomised into a control group... and a treatment group..."
Allocation concealment?	Low risk	"Randomisation was made through a central office and was based on the use of randomised permuted blocks, with stratification to ensure that appropriate balance between the treatment groups was maintained at each centre"

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Callam 1987 (*Continued*)

Blinding? Ulcer healing	High risk	Participants and personnel not blinded. Outcome assessors: tracings of the ulcer circumference were completed by people who were not blind to treatment group, however, analysis of the tracings (calculation of percentage area ulcer remaining) was blinded to treatment group: "The tracings were identified only by a code number to exclude observer bias..."
Incomplete outcome data addressed? Ulcer healing	Low risk	Similar numbers withdrew from treatment groups for similar reasons; treated as censored except for the two patients in the non-US group who withdrew due to deterioration and were regarded as unhealed by study authors
Free of selective reporting?	Unclear risk	Expected outcomes reported, though did not request a study protocol
Free of other bias?	Low risk	

Dolibog 2008

Methods	Patients who had undergone venous surgery were randomised to receive US plus standard care or standard care alone
Participants	70 post venous-surgery patients whose venous disease was diagnosed by Duplex scan (to rule out arterial disease and locate the venous insufficiency). 33 participants received US plus standard care and 37 received standard care alone. Excluded people with diabetes, and rheumatoid arthritis
Interventions	US group: US via a water bath at 0.5 W/cm²; 1 MHz frequency, US probe 10cm² placed 2 cm above ulcer. An ulcer of 5 cm² or less had 5 min treatment with one minute extra of treatment per 1 cm² over the 5cm^2 area. Treatment daily for six days per week for seven weeks. Between treatments ulcers were covered with saline-soaked gauze, received compression and 1 g flavonoid fraction daily. US commenced 5 days after surgery. Standard care group: saline soaks, compression, 1 g flavonoid fraction daily
Outcomes	Proportion of ulcers completely healed.
Notes	Ulcers were observed for complete healing and measured for area, volume and a range of dimensions using planimetry. Duration of follow-up: seven weeks.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

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Dolibog 2008 (*Continued*)

Adequate sequence generation?	Unclear risk	"70 patients ... were included and allocated into two comparative groups". "A prospective, randomised, controlled clinical trial was conducted..."
Allocation concealment?	Unclear risk	Not mentioned. See above.
Blinding? Ulcer healing	High risk	Participants: not blinded, since they did not receive sham US. Personnel: unclear, but presumably not blinded since not sham controlled. Outcome assessors: unclear. "Treatment progress was evaluated by observing the number of completely healed ulcers, and measuring the area ... by planimetry...".
Incomplete outcome data addressed? Ulcer healing	Unclear risk	Final numbers not stated; complete follow-up implied.

Eriksson 1991

Methods	Randomised trial comparing US plus standard care with sham US plus standard care
Participants	Patients with venous leg ulcers referred from departments of internal medicine and surgery, and primary care providers. People were excluded if they were allergic to the standard treatment, or if they had evidence of peripheral arterial disease; rheumatoid arthritis; diabetic ulcers; or traumatic venous ulcers
Interventions	US group: US 1 W/cm² at 1 MHz, for 10 min twice a week for 8 weeks, plus standard treatment (n = 19). Sham US group: standard treatment plus sham US as above but with no output. Standard care comprised cleansing with saline; paste bandage, support bandage plus exercise advice (n = 19)
Outcomes	Number of ulcers known to be completely healed at 8 weeks (of those randomised). % ulcer area healed at 8 weeks (SD). Withdrawals with reasons, and by group.
Notes	Duration of follow-up: 8 weeks.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	"... patients were randomly assigned to either a control group ... or a treatment group..."

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Eriksson 1991 (*Continued*)

Allocation concealment?	Unclear risk	See above.
Blinding? Ulcer healing	Unclear risk	Participants: this is a "placebo" (sham) US controlled trial, therefore, it is implied that the participants did not know their allocation. Personnel: unclear (they may have been responsible for setting the ultrasound machine to zero). Outcome assessors: unclear whether those responsible for taking ulcer tracings were blinded. Those responsible for analysing the tracings were blinded: "At the end of the 8 week study all tracings were analysed using a computer graphics program to calculate the areas of each ulcer...The tracings were identified by code numbers to exclude observer bias."
Incomplete outcome data addressed? Ulcer healing	Unclear risk	38 people randomised; 13 withdrew. Not clear how these were handled: "The cumulative percentage of healed ulcers in the two groups was compared by the use of life table methods" (censoring not mentioned). In the Results section: "If analysed by intention to treat there were similar non-significant findings between the groups"

Franek 2004

Methods	Randomised trial comparing two US densities (0.5 W/cm² and 1 W/cm²) with no US and pharmacotherapy
Participants	65 patients with signs of venous disease and an ABPI > 1.0, were admitted to dermatology departments. People were excluded if they had diabetes mellitus or advanced sclerosis. US group 1 (1 W/cm²): n = 22; US group 2 (0.5 W/cm²): n = 21; Pharmacotherapy group: n = 22. Mean (median) baseline area (cm²): US group 1: 15.62 (12.51); US group 2: 15.57 (6.71); Pharmacotherapy group: 23.74 (11.72). The authors did not publish the SD or SE around the mean.
Interventions	US group 1: pulsed 1 MHz, 1 W/cm² in a water bath with a temperature of 34 °C plus standard treatment of topical wet dressings of isotonic salt solution and compression therapy. Patients were admitted to the Dermatology Clinic of the Silesian Medical University in Katowice.

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	US group 2: pulsed 1 MHz, 0.5 W/cm² in a water bath with a temperature of 34 °C plus standard treatment of topical wet dressings of isotonic salt solution and compression therapy. Patients were admitted to the Dermatology Clinic of the Silesian Medical University in Katowice. Pharmacotherapy group: topical pharmacotherapy including potassium permanganate local baths, wet dressing of 0.1 copper sulphate solution, compresses of fibrolan, chloramphenicol, colistin, gentamicin plus compressive therapy. Patients were hospitalised in the Dermatology Department of Hospital No. 2 in Zabrze These 3 treatment groups differed systematically not only in the US treatment but the pharmacotherapy received by the Pharmacotherapy group and its place of treatment (different from that of the US groups)
Outcomes	Number of ulcers completely healed at 3 weeks. Average weekly rate of ulcer area reduction (% per week).
Notes	No withdrawals reported. "Planimetric measurements of homothetic, congruent projections of the ulcerated areas using a digitising tablet. Ulcer depth measured ...with a precision built mechanical micrometer..." Duration of follow-up: 3 weeks.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	"A total of 65 patients with venous ulcers were randomly divided into three groups.. ."
Allocation concealment?	Unclear risk	See above.
Blinding? Ulcer healing	High risk	Participants: no (no sham US). Personnel: no; the control patients were treated in a different hospital. Outcome assessors: no: "To check how the ulcers healed we measured the longest dimensions ... and the widest dimensions perpendicular to the former ... measurements were taken before the treatment, every week during treatment and upon completion..."
Incomplete outcome data addressed? Ulcer healing	Unclear risk	Complete follow-up implied but not stated. No mention of ITT
Free of other bias?	High risk	Major performance bias. Control group patients (Pharmacotherapy group) received topical ulcer treatments that were not received by the US patients, and they were admitted to a different hospital

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Lundeberg 1990

Methods	An RCT of directly-applied, high-frequency US in 44 leg ulcer patients compared with sham US
Participants	44 patients with venous leg ulcers referred from departments of internal medicine, surgery, and primary care. Exclusion criteria: peripheral vascular disease, rheumatoid arthritis, diabetes mellitus, or traumatic venous ulcer. US group: n = 22; Sham US group: n = 22.
Interventions	US group: US 0.5 W/cm², at 1 MHz for 10 min. US was applied to the ulcer and surrounding tissue. Treatment frequency: 3 times a week for 4 weeks, twice a week for 4 weeks, and once weekly for 4 weeks, unless healing had occurred. Patients also received standard treatment (see below). Sham US group: sham US plus standard treatment of ulcer cleansed with saline, application of paste bandage, support bandage and advice on exercise from a standard instruction sheet
Outcomes	Number of ulcers completely healed at 12 weeks. Mean % of initial ulcer area remaining at 12 weeks. Withdrawals by group, with reasons.
Notes	Duration of follow-up: 12 weeks.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	"The patients were randomly assigned... The distribution of the patients was based on the use of randomised permuted blocks"
Allocation concealment?	Unclear risk	Not mentioned.
Blinding? Ulcer healing	Unclear risk	Participants: yes (sham compared with active). Personnel: unclear whether they were responsible for setting the ultrasound machine to zero Outcome assessors: unclear whether person taking the ulcer tracing was aware of allocation. Person analysing the tracing was blinded: "At the end of the 12 week study all tracings were analysed using a computer graphics program to calculate the areas of each ulcer... tracings were identified by code numbers to exclude observer bias"

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Lundeberg 1990 (*Continued*)

Incomplete outcome data addressed? Ulcer healing	High risk	44 participants were randomised; 12 withdrew (evenly distributed between groups and for similar reasons). "Patients refused to continue or withdrew from the study for any of the following reasons: allergy to treatment; excessive pain; intervening illness...". The analysis was by "life table methods" but it is not clear if withdrawn patients were censored; in the results: "The lack of difference was also maintained when taking withdrawals into consideration. If analysed by intention to treat there were similar non-significant findings..." suggesting not

Peschen 1997

Methods	People attending an outpatients' clinic were randomised to receive either US (indirect method) plus standard treatment or sham US plus standard treatment
Participants	24 patients attending outpatient clinic, with venous leg ulcer of minimum area 2 cm^2, and minimum duration of 3 months. Clinical diagnosis of venous disease confirmed by history, Doppler US, light reflection rheography, ABPI $\geq$ 0.8. Excluded people with arterial disease, liver disease, cardiac or renal insufficiency, haemorrhagic gastroduodenitis, colitis, leukaemia, diabetes, rheumatoid arthritis, treatment allergy. US group: n= 12; Sham US group: n= 12. Mean ulcer area (cm^2) (SD): US group: 15.67 (19.91); Sham US group: 19.94 (17.11). Mean ulcer duration (SD) (months): US group: 5.5 (3.2); Sham US group: 4.5 (1.1).
Interventions	US group:US 30 kHz, at 0.1 W/cm^2 for 10 min 3 times a week plus standard therapy (comprised hydrocolloid dressings, "strong" compression therapy). The US was delivered by placing legs in a footbath of water at 32-34 °C filled to 10 cm above the ulcer. The US probe was immersed in the bath 5 cm from the ulcer. Continuous US given for 10 min. Sham US group: sham US plus standard therapy.
Outcomes	The ulcer was measured using planimetry at 2, 4, 6, 8, 10, 12 weeks. The initial ulcer radius was calculated from the initial area and thereafter the daily ulcer radius reduction calculated at each time. Photographs were taken at the same time points. Ulcers completely healed at 12 weeks. Mean % decrease in ulcer area at 12 weeks. Adverse events: micro bleeding and pain around the ulcer. Withdrawals by group and with reasons.

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Peschen 1997 (*Continued*)

Notes	No variance data supplied for continuous outcomes. Duration of follow-up: 12 weeks.	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	"Patients were randomised in parallel groups ...".
Allocation concealment?	Unclear risk	See above; no further information.
Blinding? Ulcer healing	Unclear risk	Participants: yes, sham controlled. Personnel: almost certainly not: "The same procedure was selected for the placebo treatment, but no ultrasound was generated during the 10 min footbath". Outcome assessors: unclear: "the ulcer area was measured using planimetry ... prior to treatment and after 2, 4, 6, 8, 10 and 12 weeks of therapy"
Incomplete outcome data addressed? Ulcer healing	High risk	Two patients (both control group) were withdrawn due to "non-compliance"

Taradaj 2008

Methods	Patients assessed as having venous disease by assessment of symptoms and Duplex scanning, to rule out arterial disease, were offered venous surgery. Surgery included, as appropriate to each patient, crossectomy, partial stripping of the greater or lesser saphenous veins, local phlebectomy and ligation of insufficient perforators. Post surgical patients were randomised to receive US (indirect, water-bath method) or standard care. Patients who refused surgery were also randomised to US or standard care
Participants	Duplex scanning ruled out arterial disease. All patients had symptoms of chronic venous insufficiency Baseline characteristics: Mean duration of ulcer (months) (SD): Group 1: 32.04 (22.12) n = 21; Group 2: 32.89 (20.89) n = 20; Group 3: 30.99 (20.09) n = 20; Group 4: 30.87 (20.12) n = 20. Mean baseline area (cm^2) (SD): Group 1: 18.66 (10.22); Group 2: 18.02 (10.72); Group 3: 17.07 (10.42); Group 4: 18.06 (11.09).

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Interventions	Group 1 (n = 21): surgery plus US, compression stockings (Sigvaris, 30-40 mmHg at ankle), drug therapy. Group 2 (n = 20): surgery plus compression and drug therapy. Group 3 (n = 20): US compression and drug therapy. Group 4 (n = 20): compression and drug therapy. Group 1 compared with Group 2 Group 3 compared with Group 4 US 0.5W/cm² pulsed; impulse 2 mS, interval 8 mS. Frequency 1 MHz. Performed in a bath of water with temp 34 °C. Probe head 10 cm² placed 2 cm above ulcer. An ulcer of 5 cm² or less had 5 min treatment. 1 min more treatment for each 1 cm² greater than this size. Treatment daily for 6 days/week for 7 weeks. Drug therapy was flavonoid (450 mg diosmin, 50 mg hesperidin), twice daily. Ulcers covered by saline soaks. Dressings changed once daily only in clinic
Outcomes	Treatment progress evaluated by observation of number of healed ulcers, measuring area by planimetry by projecting image onto transparency paper using a digitising pallet. Measurements of area and volume before at baseline, treatment each week
Notes	Duration of follow-up 7 weeks.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	"In this randomised controlled clinical trial...". Method of randomisation not stated
Allocation concealment?	Unclear risk	"Eighty one patients with venous leg ulcers were included...Forty one individuals - who agreed on surgical operation ... were ultimately allocated into two comparative groups 1 and 2. Other individuals - who did not agree on surgical procedure - were ultimately allocated into two comparative groups 3 and 4..."
Blinding? Ulcer healing	High risk	Participants: no since not sham controlled. Personnel: no, see above. Outcome assessors: almost certainly not: "Treatment progress was evaluated by observation of the number of completely healed ulcers, and measuring the area of the ulceration by planimetry of congruent projections of these wounds onto transparency paper using a digitizing pallet...Measurements of area and volume were performed one each person before and after therapy... "

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Incomplete outcome data addressed? Ulcer healing	Unclear risk	Not mentioned. Withdrawals not mentioned (100% follow up implied but not stated)

Weichenthal 1997

Methods	Patients admitted to an outpatients clinic for chronic leg ulceration randomised between 0.1 W/cm² US via the indirect (water-bath) method plus conventional therapy or conventional therapy alone
Participants	38 patients with chronic venous leg ulceration of minimum duration of 3 months plus evidence of incompetent perforating or superficial veins US group:n =19; Conventional therapy group: n = 18.
Interventions	US group: 30 kHz of US, intensity 100 mW/cm² for 10 min, plus conventional therapy. Conventional therapy group: conventional therapy of fibrinolytic agents, antibiotics, or other antiseptic agents, "generally compression therapy performed with elastic bandages"
Outcomes	Number of ulcers healed at eight weeks. Mean % of initial ulcer area present at 8 weeks. Withdrawals by group and with reasons. Adverse events reported as pain and erythema (and reported for US group only)
Notes	Duration of follow-up: 8 weeks.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	"Each patient was randomly assigned to receive...". "Randomisation was performed with sequential treatment cards which labelled the patient as either control or treatment. The cards were produced with a computer random number generator, preserving balance for each group"
Allocation concealment?	Unclear risk	See above.
Blinding? Ulcer healing	High risk	Participants: no since not sham controlled. Personnel: see above. Outcome assessors: highly unlikely: "After each treatment, local findings and side effects of the conventional or of the ultrasound treatment were recorded...The ulcerated area was measured by planimetry after

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Weichenthal 1997 (*Continued*)

		3 and 8 weeks..."
Incomplete outcome data addressed? Ulcer healing	Unclear risk	1 ineligible patient excluded from the analysis: "Within the control group only 18 patients were evaluated for the study endpoints because at the end of the study evidence of arterial vascular disease was present in one patient, who was therefore excluded from the evaluation." Otherwise complete follow up and analysis by ITT implied, but not stated

Abbreviations
> = greater than
≥ = greater than or equal to
ITT = intention-to-treat analysis
min = minute(s)
n = number of participants in group(s)
RCT = randomised controlled trial
SD = standard deviation
US = ultrasound

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

Study	Reason for exclusion
Dissemond 2003	Not a trial.
Dyson 1976	Not a randomised trial.
Kavros 2007a	Trial involved predominantly people with ulcers secondary to critical limb ischaemia
Kavros 2007b	Trial was an open-label, non-randomised, baseline-controlled clinical case series
Roche 1984	Not a randomised trial.
Tan 2007	Non-controlled pilot study.

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Characteristics of studies awaiting assessment *[ordered by study ID]*

Franek 2006

Methods	
Participants	
Interventions	
Outcomes	
Notes	In Polish, awaiting translation.

Taradaj 2007

Methods	
Participants	
Interventions	Comparison of sonotherapy with compression therapy.
Outcomes	
Notes	Paper published in Polish; awaiting translation.

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

Nelson 2006

Trial name or title	Multicentre randomised controlled trial comparing the clinical effectiveness of weekly US combined with standard care in the treatment of 'hard-to-heal' venous leg ulcers
Methods	RCT
Participants	People with chronic venous leg ulcers.
Interventions	Directly-applied, high-frequency US delivered once per week plus standard care compared with standard care alone
Outcomes	Time to ulcer healing, quality of life, adverse events, costs
Starting date	2005
Contact information	Dr Jude Watson, York Trials Unit, Department of Health Sciences, University of York, UK
Notes	Likely to be published late 2010.

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DATA AND ANALYSES

Comparison 1. Ultrasound (any frequency) vs no ultrasound

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion of ulcers healed at 7 or 8 weeks	6		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 2. High frequency US vs no ultrasound

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion of ulcers completely healed during study follow up (varying durations of follow up)	6	406	Risk Ratio (M-H, Random, 95% CI)	1.34 [0.99, 1.80]
2 Proportion ulcers completely healed at 3 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3 Proportion ulcers completely healed at 7 or 8 weeks	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Losses as failures	5	341	Risk Ratio (M-H, Fixed, 95% CI)	1.40 [1.00, 1.96]
3.2 Complete case analysis	5	290	Risk Ratio (M-H, Fixed, 95% CI)	1.36 [0.98, 1.88]
4 Proportion of ulcers completely healed at 12 weeks	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 High-frequency US (losses as failures)	2	152	Risk Ratio (M-H, Fixed, 95% CI)	1.47 [0.99, 2.20]
4.2 High-frequency US (complete case analysis)	2	114	Risk Ratio (M-H, Fixed, 95% CI)	1.35 [0.94, 1.93]

Comparison 3. Low frequency US vs no ultrasound

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion ulcers completely healed at 8 - 12 weeks	2	61	Risk Ratio (M-H, Fixed, 95% CI)	3.91 [0.47, 32.85]

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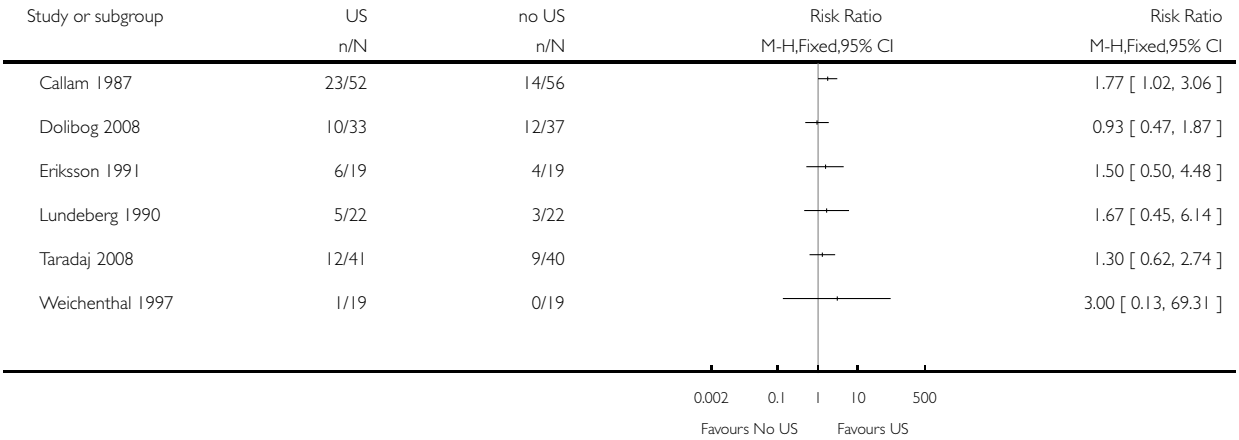
Analysis 1.1. Comparison 1 Ultrasound (any frequency) vs no ultrasound, Outcome 1 Proportion of ulcers healed at 7 or 8 weeks.

Review: Therapeutic ultrasound for venous leg ulcers

Comparison: 1 Ultrasound (any frequency) vs no ultrasound

Outcome: 1 Proportion of ulcers healed at 7 or 8 weeks



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Analysis 2.1. Comparison 2 High frequency US vs no ultrasound, Outcome 1 Proportion of ulcers completely healed during study follow up (varying durations of follow up).

Review: Therapeutic ultrasound for venous leg ulcers

Comparison: 2 High frequency US vs no ultrasound

Outcome: 1 Proportion of ulcers completely healed during study follow up (varying durations of follow up)

Study or subgroup	US n/N	No US n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Callam 1987	25/52	17/56		38.1 %	1.58 [0.97, 2.58]
Dolibog 2008	10/33	12/37		18.7 %	0.93 [0.47, 1.87]
Eriksson 1991	6/19	4/19		7.5 %	1.50 [0.50, 4.48]
Franek 2004	4/43	1/22		2.0 %	2.05 [0.24, 17.23]
Lundeberg 1990	10/22	8/22		17.5 %	1.25 [0.61, 2.56]
Taradaj 2008	12/41	9/40		16.2 %	1.30 [0.62, 2.74]
Total (95% CI)	**210**	**196**		**100.0 %**	**1.34 [0.99, 1.80]**

Total events: 67 (US), 51 (No US)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.72$, df = 5 (P = 0.89); $I^2 = 0.0\%$

Test for overall effect: Z = 1.88 (P = 0.059)

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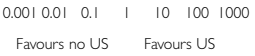
Analysis 2.2. Comparison 2 High frequency US vs no ultrasound, Outcome 2 Proportion ulcers completely healed at 3 weeks.

Review: Therapeutic ultrasound for venous leg ulcers

Comparison: 2 High frequency US vs no ultrasound

Outcome: 2 Proportion ulcers completely healed at 3 weeks

Study or subgroup	US n/N	No US n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Franek 2004	4/43	1/22			2.05 [0.24, 17.23]
Subtotal (95% CI)	**0**	**0**			**0.0 [0.0, 0.0]**
Total events: 4 (US), 1 (No US)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.0 (P < 0.00001)					



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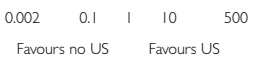
Analysis 2.3. Comparison 2 High frequency US vs no ultrasound, Outcome 3 Proportion ulcers completely healed at 7 or 8 weeks.

Review: Therapeutic ultrasound for venous leg ulcers

Comparison: 2 High frequency US vs no ultrasound

Outcome: 3 Proportion ulcers completely healed at 7 or 8 weeks

Study or subgroup	US n/N	No US n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Losses as failures					
Callam 1987	23/52	14/56		33.0 %	1.77 [1.02, 3.06]
Dolibog 2008	10/33	12/37		27.7 %	0.93 [0.47, 1.87]
Eriksson 1991	6/19	4/19		9.8 %	1.50 [0.50, 4.48]
Lundeberg 1990	5/22	3/22		7.3 %	1.67 [0.45, 6.14]
Taradaj 2008	12/41	9/40		22.3 %	1.30 [0.62, 2.74]
Subtotal (95% CI)	**167**	**174**		**100.0 %**	**1.40 [1.00, 1.96]**
Total events: 56 (US), 42 (No US)					
Heterogeneity: Chi^2 = 2.12, df = 4 (P = 0.71); I^2 =0.0%					
Test for overall effect: Z = 1.95 (P = 0.051)					
2 Complete case analysis					
Callam 1987	23/41	14/41		33.8 %	1.64 [0.99, 2.72]
Dolibog 2008	10/33	12/37		27.3 %	0.93 [0.47, 1.87]
Eriksson 1991	6/12	4/13		9.3 %	1.63 [0.60, 4.38]
Lundeberg 1990	5/17	3/15		7.7 %	1.47 [0.42, 5.14]
Taradaj 2008	12/41	9/40		22.0 %	1.30 [0.62, 2.74]
Subtotal (95% CI)	**144**	**146**		**100.0 %**	**1.36 [0.98, 1.88]**
Total events: 56 (US), 42 (No US)					
Heterogeneity: Chi^2 = 1.81, df = 4 (P = 0.77); I^2 =0.0%					
Test for overall effect: Z = 1.85 (P = 0.064)					



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Analysis 2.4. Comparison 2 High frequency US vs no ultrasound, Outcome 4 Proportion of ulcers completely healed at 12 weeks.

Review: Therapeutic ultrasound for venous leg ulcers

Comparison: 2 High frequency US vs no ultrasound

Outcome: 4 Proportion of ulcers completely healed at 12 weeks

Study or subgroup	US n/N	No US n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 High-frequency US (losses as failures)					
Callam 1987	25/52	17/56		67.2 %	1.58 [0.97, 2.58]
Lundeberg 1990	10/22	8/22		32.8 %	1.25 [0.61, 2.56]
Subtotal (95% CI)	**74**	**78**		**100.0 %**	**1.47 [0.99, 2.20]**
Total events: 35 (US), 25 (No US)					
Heterogeneity: Chi^2 = 0.29, df = 1 (P = 0.59); I^2 =0.0%					
Test for overall effect: Z = 1.89 (P = 0.059)					
2 High-frequency US (complete case analysis)					
Callam 1987	25/41	17/41		66.7 %	1.47 [0.95, 2.28]
Lundeberg 1990	10/17	8/15		33.3 %	1.10 [0.59, 2.05]
Subtotal (95% CI)	**58**	**56**		**100.0 %**	**1.35 [0.94, 1.93]**
Total events: 35 (US), 25 (No US)					
Heterogeneity: Chi^2 = 0.56, df = 1 (P = 0.46); I^2 =0.0%					
Test for overall effect: Z = 1.64 (P = 0.10)					

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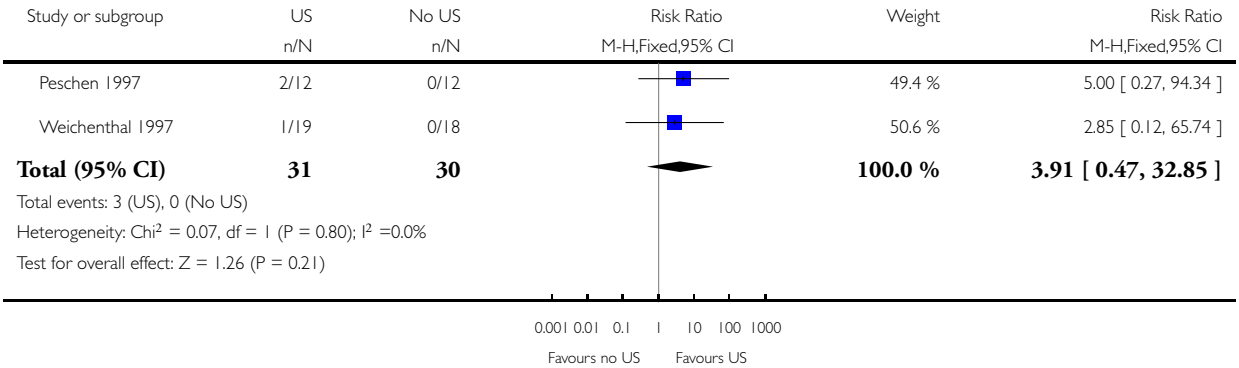
Analysis 3.1. Comparison 3 Low frequency US vs no ultrasound, Outcome 1 Proportion ulcers completely healed at 8 - 12 weeks.

Review: Therapeutic ultrasound for venous leg ulcers

Comparison: 3 Low frequency US vs no ultrasound

Outcome: 1 Proportion ulcers completely healed at 8 - 12 weeks



APPENDICES

Appendix 1. Search strategy for the original review 1999

For the original review the Cochrane Wounds Group Specialised Register was searched for RCTs of therapeutic ultrasound until December 1999. The reference lists of reviews and papers obtained from this search were scrutinised to identify additional studies.

Appendix 2. Search strategy for the first update 2007

For the original review the Cochrane Wounds Group Specialised Register was searched for RCTs of therapeutic ultrasound until December 1999. The reference lists of reviews and papers obtained from this search were scrutinised to identify additional studies.
For this update we performed a search of the Cochrane Wounds Group Specialised Register (last searched 10/08/07). Trials on the register are identified by hand searching of relevant journals, conference proceedings, and searching electronic databases. We carried out an additional search of the following electronic databases:
The Cochrane Central Register of Controlled Trials (CENTRAL) - *The Cochrane Library* Issue 3, 2007
Ovid MEDLINE - 1950 to July Week 4 2007
Ovid EMBASE - 1980 to 2007 Week 31
Ovid CINAHL - 1982 to August Week 1 2007
We searched The Cochrane Central Register of Controlled Trials (CENTRAL) using the following strategy, which was adapted for other databases where appropriate:
#1 MeSH descriptor Varicose Ulcer explode all trees
#2 MeSH descriptor Leg Ulcer explode all trees
#3 (varicose NEXT ulcer*) or (venous NEXT ulcer*) or (leg NEXT ulcer*) or (foot NEXT ulcer*) or (stasis NEXT ulcer*)
#4 (#1 OR #2 OR #3)

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#5 MeSH descriptor Ultrasonic Therapy explode all trees
#6 ultrasound NEAR/5 therap*
#7 ultrason* NEAR/5 therap*
#8 (#5 OR #6 OR #7)
#9 (#4 AND #8)
The MEDLINE search was combined with the Cochrane highly sensitive search strategy for identifying reports of randomized controlled trials (Higgins 2005). The EMBASE and CINAHL searches were combined with the trial filters developed by the Scottish Intercollegiate Guidelines Network (SIGN).
We contacted researchers to obtain any unpublished data when needed. Reference lists of potentially useful articles were also searched. There was no restriction by language, date or publication status.

Appendix 3. Ovid MEDLINE search strategy

1 exp Leg Ulcer/
2 (varicose ulcer* or venous ulcer* or leg ulcer* or foot ulcer* or (feet adj ulcer*) or stasis ulcer* or (lower extremit* adj ulcer*) or crural ulcer* or ulcus cruris).tw.
3 or/1-2
4 exp Ultrasonic Therapy/
5 (ultrasound adj5 therap*).tw.
6 (ultrason* adj5 therap*).tw.
7 or/4-6
8 3 and 7

Appendix 4. Ovid EMBASE search strategy

1 exp Leg Ulcer/
2 (varicose ulcer* or venous ulcer* or leg ulcer* or foot ulcer* or (feet adj ulcer*) or stasis ulcer* or (lower extremit* adj ulcer*) or crural ulcer* or ulcus cruris).tw.
3 or/1-2
4 exp Ultrasonic Therapy/
5 (ultrasound adj5 therap*).tw.
6 (ultrason$ adj5 therap*).tw.
7 or/4-6
8 3 and 7

Appendix 5. EBSCO CINAHL search strategy

s10 S4 and S9
S9 S5 or S6 or S7 or S8
S8 TI ultrason* N5 therap* or AB ultrason* N5 therap*
S7 TI ultrasound N5 therap* or AB ultrasound N5 therap*
S6 (MH "Ultrasonics")
S5 (MH "Ultrasonic Therapy")
S4 S1 or S2 or S3
S3 TI lower extremity N3 ulcer* or AB lower extremity N3 ulcer*
S2 TI (varicose ulcer* or venous ulcer* or leg ulcer* or foot ulcer* or (feet N1 ulcer*) or stasis ulcer* or crural ulcer*) or AB (varicose ulcer* or venous ulcer* or leg ulcer* or foot ulcer* or (feet N1 ulcer*) or stasis ulcer* or crural ulcer*)
S1 (MH "Leg Ulcer+")

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Appendix 6. *Criteria for judgments for the sources of bias*

1. Was the allocation sequence randomly generated?

Yes, 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.

No, 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 judgement of 'Yes' or 'No'.

2. Was the treatment allocation adequately concealed?

Yes, 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.

No, 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 were 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 to permit judgement of 'Yes' or 'No'. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement, 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?

Yes, 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 unlikely to introduce bias.

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No, 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 likely to introduce bias.

Unclear

Any one of the following:

- Insufficient information to permit judgement of 'Yes' or 'No'.
- The study did not address this outcome.

4. Were incomplete outcome data adequately addressed?

Yes, 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.

No, 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 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 enough to induce clinically relevant bias in observed effect size.
- 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation.
- Potentially inappropriate application of simple imputation.

Unclear

Any one of the following:

- Insufficient reporting of attrition/exclusions to permit judgement of 'Yes' or 'No' (e.g. number randomized 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?

Yes, low risk of bias

Any of the following:

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- 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)

No, 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 is 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 to permit judgement of 'Yes' or 'No'. It is likely that the majority of studies will fall into this category.

6. Other sources of potential bias:

Yes, low risk of bias

The study appears to be free of other sources of bias.

No, 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.

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WHAT'S NEW

Last assessed as up-to-date: 7 May 2010.

Date	Event	Description
9 November 2011	Amended	Contact details updated.

HISTORY

Protocol first published: Issue 4, 1998

Review first published: Issue 4, 2000

Date	Event	Description
7 May 2010	New citation required and conclusions have changed	The review has been substantially re-written and re-structured. We have re-structured the review to distinguish high and low frequency ultrasound. We have also added a summary of findings table
7 May 2010	New search has been performed	New searches have been conducted and two new studies added to the review (Dolibog 2008; Taradaj 2008). Two previously included trials have now been excluded as they were quasi-randomised (Dyson 1976; Roche 1984) .
30 April 2008	Amended	Converted to new review format.
2 November 2007	New citation required and conclusions have changed	Substantive amendment. For this first update, new searches were carried out in August 2007 and one new trial met the inclusion criteria for the review (Franek 2004). Additional citations were identified for existing trials and these were added to the appropriate reference lists. One trial (Franek 2006) is currently awaiting assessment, it has been translated but clarification has been sought from the author as to whether this trial is a further publication of Franek 2004

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CONTRIBUTIONS OF AUTHORS

NC was a co-author of the original review and re-extracted the data, assessed risk of bias, undertook the analysis, compiled the summary of findings table and drafted this update.

DAK checked the search results for the updated search, identified new studies for inclusion, extracted data, undertook quality assessment of all included studies, undertook the analysis and drafted the previous update.

SBS checked the inclusion/exclusion decisions and data extraction, undertook the analysis and helped draft the final update.

DECLARATIONS OF INTEREST

NC is a co-investigator on an ongoing RCT of therapeutic ultrasound for venous leg ulcers. Nicky Cullum and Sally Bell-Syer are members of the Wounds Group Editorial team and as a result Andrea Nelson (Editor) approved the final version of the review update for publication.

SOURCES OF SUPPORT

Internal sources

- Department of Health Sciences, University of York, UK.

External sources

- NHS Health Technology Assessment Programme, UK.
- North Yorkshire & East Coast Foundation School, UK.

INDEX TERMS

Medical Subject Headings (MeSH)

*Ultrasonic Therapy [economics]; Quality of Life; Randomized Controlled Trials as Topic; Treatment Outcome; Varicose Ulcer [*therapy]; Wound Healing [physiology]

MeSH check words

Humans

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