Therapeutic ultrasound for acute ankle sprains

M. P. J. VAN DEN BEKEROM¹, D. A. W. M. VAN DER WINDT²
G. TER RIET³, G. J. VAN DER HEIJDEN⁴, L. M. BOUTER⁵

Background. Ultrasound is used in the treatment of a wide variety of musculoskeletal disorders, which include acute ankle sprains.

Aim. To evaluate the effects of ultrasound therapy in the treatment of acute ankle sprains.

Methods. We searched the Cochrane Bone, Joint and Muscle Trauma Group Specialised Register, the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE until September 2010, CINAHL (until 2004), and PEDro (accessed 01/06/09). (Quasi)-randomised trials were included if the following conditions were met: at least one study group was treated with therapeutic ultrasound; participants had acute lateral ankle sprains; and outcome measures included general improvement, pain, swelling, functional disability, or range of motion. Risk ratios and risk differences with 95% confidence intervals were calculated for dichotomous outcomes and mean differences with 95% confidence intervals for continuous outcome measures. Limited pooling of data was undertaken where there was clinical homogeneity in terms of participants, treatments, outcomes, and follow-up time points.

Results. Six trials were included, involving 606 participants. Five trials included comparisons of ultrasound therapy with sham ultrasound; and three trials included single comparisons of ultrasound with three other treatments. None of the five placebo-controlled trials (sham ultrasound) demonstrated differences between true and sham ultrasound therapy for any outcome measure at one to four weeks of follow-up. The pooled risk ratio for general improvement at one week was 1.04 (random-effects model, 95% confidence interval 0.92 to 1.17) for active *versus* sham ultrasound. The differences between intervention groups were gener-

¹Department of Orthopedic Surgery, Spaarne Hospital, Hoofddorp, the Netherlands

²Arthritis Research UK Primary Care Centre
Institute for Primary Care and Health Sciences, Keele University, Keele, UK

³Academic Medical Center
Department General Practice, Amsterdam, the Netherlands

⁴Julius Center for Health Sciences and Primary Care
University Medical Center Utrecht, Utrecht, the Netherlands

⁵Executive Board, VU University Medical Center, Amsterdam, the Netherlands

ally small, between 0% and 6%, for most dichotomous outcomes.

Conclusion. The evidence from the five small placebo-controlled trials included in this review does not support the use of ultrasound in the treatment of acute ankle sprains. The potential treatment effects of ultrasound appear to be generally small and probably of limited clinical importance, especially in the context of the short-term recovery period in most people with these injuries. However, the available evidence is insufficient to rule out the possibility that there is an optimal dosage schedule for ultrasound therapy that may be of benefit.

KEY WORDS: Ankle - Ligaments - Wounds and injuries.

Acute soft tissue injuries of the ankle, involving simple stretching, partial rupture or complete rupture of at least one ligament, are among the most common sports injuries. These injuries result in high costs to society as a result of work absence and health care resource use. There are uncertainties regarding the optimal treatment of acute ankle injuries, and ankle sprains may be associated with long-term complaints

Corresponding author: M. P. J. van den Bekerom, Spaarne Hospital, Department of Orthopaedic Surgery, Spaarnepoort 1, P.O. Box 22660, 2130 AT Hoofddorp, the Netherlands.
E-mail: bekerom@gmail.com

We aimed to determine whether ultrasound therapy is more effective than reference treatments (placebo intervention, no treatment, or other types of interventions) in people with acute ankle sprains with respect to the following outcomes: general recovery, improvement of pain relief, swelling, functional disability, and range of motion. This paper is based on three previous published reviews.¹²⁻¹⁴

Criteria for considering studies for this review

Trials using at least one of the following six types of outcome measures were considered for inclusion: 1) general improvement (patient perceived benefit, proportion/percentage of participants recovered, etc.); 2) improvement of pain (visual analogue scale, ordinal scale, pain questionnaire); 3) swelling; 4) functional disability (ability to walk, sick leave, re-uptake of sports, multiple item questionnaire to report activity limitations); 5) range of motion; 6) and adverse events (although highly unlikely, data on any adverse event following treatment with therapeutic ultrasound were sought).

We searched the Cochrane Bone, Joint and Muscle Trauma Group Specialised Register (September 2010), the Cochrane Central Register of Controlled Trials (The Cochrane Library 2010, Issue 3), MEDLINE (1966 to September 2010), EMBASE (1983 to September 2010), CINAHL (1982 to July 2004), and PEDro - the Physiotherapy Evidence Database (accessed 01/06/09) (Table I). We also searched the Cochrane Rehabilitation and Related Therapies Field database using the search term 'ultrasound' (June 2009). The WHO International Clinical Trials Registry Platform was searched for ongoing trials. No language restrictions were applied.

The reference lists of all retrieved articles were screened, and we contacted colleagues to identify additional relevant publications.

TABLE I.—*Search strategy for Medline.*

1. Ankle injuries/
2. Ankle/or ankle joint/or lateral ligament, ankle/
3. or/1-2
4. "Sprains and strains"
5. ankle\$1.tw
6. and/4-5
7. or/3,6
8. Ultrasonics/
9. (ultrasound or ultrasonic \$1).tw.
10. or/8-9
11. and/7,10
12. Randomized controlled trial.pt.
13. Controlled clinical trial.pt.
14. randomized.ab.
15. placebo.ab.
16. Drug therapy.fs.
17. randomly.ab.
18. trial.ab.
19. groups.ab.
20. or/12-19
21. exp Animals/not Humans/
22. 20 not 21
23. and/11,22

Data collection and analysis

Two authors independently applied the selection criteria to the publications identified by the search strategy described above. During consensus meetings, remaining disagreements were discussed and a third author was consulted in cases of remaining disagreement. For each publication, two authors independently extracted all necessary details using standardised forms. Results data were collected for the primary and secondary outcome measures. All publications included in the review were blinded for authors, affiliation, source, and results. Subsequently, the risk of bias was independently assessed by two authors based on 10 domains, based on the Cochrane Risk of Bias Tool and the Maastricht Amsterdam Consensus List.^{15, 16} These were scored as high, low or unclear if insufficient information was available for assessment.

Risk ratios and risk differences, together with 95% confidence intervals, were calculated for dichotomous outcomes; and mean differences, together with 95% confidence intervals, were calculated for continuous outcome measures. Whenever possible, general improvement and other dichotomous outcomes were calculated according to intention-to-treat, using the number of participants following randomization in the denominator. We assessed heterogeneity by visual inspection of the forest plot

along with consideration of the χ^2 test for heterogeneity and the I^2 statistic. Statistical pooling of results was undertaken for subsets of studies that showed statistical homogeneity and sufficient clinical homogeneity with respect to participants, interventions, outcomes, and follow-up time points using a random-effects model.^{17, 18}

Results

The search yielded nine potentially relevant trials on ultrasound therapy for acute ankle sprains. Five trials were identified in MEDLINE,^{1, 2, 19-21} Reference checking and searches in other databases resulted in the identification of four additional trials.^{4, 22-24} The two authors selecting trials for inclusion initially agreed on the status of six out of the nine trials on ankle sprains. After a consensus meeting, agreement was reached for the three remaining trials. As a result, six trials that met all the selection criteria were included in the review and the other three were excluded.

Four trials conducted in the UK were published in English,^{1, 2, 4, 19} one conducted in Denmark was published in Danish,²¹ and the last trial conducted in Malta was published in English.²⁴ These six trials involved 606 participants. All studies involved participants with acute ankle sprains of relatively short duration. Five of the six studies compared ultrasound therapy with sham ultrasound (machine turned off).^{2, 4, 19, 21, 24} Zammit and Herrington also included a no treatment control group.²⁴ In three studies, ultrasound therapy was compared with other treatment modalities: immobilisation by an elastic adhesive bandage (Elastoplast),¹ Felbinac gel, a topically applied non-steroidal anti-inflammatory drug⁴ and electrotherapy.²¹ The results of the risk of bias assessment of the individual trials are presented in Figure 1 and Table II.

Ultrasound therapy versus sham ultrasound

None of the five trials comparing ultrasound with sham ultrasound demonstrated statistically significant differences between two treatment groups for any outcome measure.^{2, 4, 19, 21, 24} The studies varied with respect to the type of ultrasound (pulsed or continuous). Sufficient information on other treatment parameters (frequency or intensity) was only

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Incomplete outcome data (attrition bias)	Baseline similarity	Blinding of care provider	Control for co-interventions	Adherence to treatment	Blinding of patients	Blinding of outcome assessment	Timing of outcome assessment
Makuloluwe 1977	?	?	?	?	+	?	?	+	+	+
Nyanzi 1999	+	?	+	?	+	+	?	+	+	+
Oakland 1993	+	?	+	?	?	+	?	+	?	+
Van Lelieveld 1979	+	?	?	?	+	+	?	+	+	+
Williamson 1986	+	?	?	?	+	?	?	+	+	+
Zammit 2005	?	?	?	+	+	+	?	+	+	+

Figure 1.—Risk of bias summary.

TABLE II.—Risk of bias assessment.

1. Random sequence generation
2. Allocation concealment
3. Incomplete outcome data
4. Baseline similarity across intervention groups
5. Blinding of care provider
6. Control for co-interventions
7. Adherence to treatment
8. Blinding of patients
9. Blinding of outcome assessment
10. Timing of outcome assessment

provided in.^{4, 19, 24} The four trials comparing active *versus* sham ultrasound treatment with follow-up periods of at least two weeks showed that the majority of participants had fully recovered at final follow-up.^{2, 19, 21, 24}

General improvement

For three studies, results of dichotomous measures of general improvement were available at seven days after randomization.^{2, 4, 21} Using the random-effects model, the pooled risk ratio (RR) for general

improvement was 1.04 (95% CI 0.92 to 1.17). The pooled risk difference (RD) in general improvement was 3.0% (95% CI -6% to 12%).

Swelling

Data from the three trials reporting on swelling could not be pooled. None of the trials found statistically significant differences between true and sham ultrasound. Nyanzi *et al.*¹⁹ found minimal difference between the two groups in ankle circumference at 14 days (51.3 cm *versus* 51.6 cm; mean difference - 0.30 cm, 95% CI -1.59 to 0.99 cm). In Van Lelieveld 1979, more participants treated with ultrasound had less than 0.5 cm difference in ankle circumference after seven days (13/ 20 *versus* 8/20, RR 1.63, 95% 0.87 to 3.04; RD 25%, 95% CI -5% to 55%). Zammit 2005 found no significant differences between the treatment groups in the mean reduction of swelling at 22 days (active 1.0 cm *versus* sham 1.3 cm).

Functional disability

Two studies (Oakland 1993; Van Lelieveld 1979) presented dichotomous data on the ability to walk or bear weight at seven days.^{4, 21} The differences between intervention groups were small (5% to 6%) and not significant. The pooled risk ratio was 1.09 (95%CI 0.92 to 1.30). The pooled risk difference for functional disability was 6% (95% CI -6% to 19%).

Range of motion

Nyanzi 1999 reported small but non-significant differences in range of motion (degrees) between true and sham ultrasound at 14 days follow-up: dorsal flexion (MD -1.80°, 95% CI -7.49 to 3.89°) and plantar flexion (MD 4.60°, 95% CI -1.67 to 10.87°).¹⁹ Zammit and Herrington observed no significant differences between the treatment groups in plantar and dorsal flexion: mean increases in plantar flexion were 4.7° in the ultrasound group and 4.6° in the sham ultrasound group; mean increases in dorsiflexion were 10° in the ultrasound group and 5.2° in the sham ultrasound group.²⁴

Adverse reactions

Adverse reactions were only reported by Oakland

1993. Eight out of 73 participants allocated to ultrasound therapy (plus placebo gel) reported 11 non-serious adverse reactions including gastrointestinal events and skin reactions.

Comparisons between ultrasound therapy and other treatment modalities

One study reported superior effects of ultrasound therapy compared with immobilisation with Elastoplast.¹ However, there were data discrepancies and the values of percentages (success) probably indicated some Elastoplast group had recovered at seven days, and 86.4% *versus* undeclared loss to follow-up from the 40 participants in each group. Makuloluwe *et al.*¹ reported that 46.2% in the ultrasound group *versus* 26.6% in the Elastoplast group had recovered at seven days, and 86.4% *versus* 58.6% at 14 days. Based on rounded up data, estimated risk difference results for success rate were 19% after one week

(95% CI -2% to 40%) and 27% after two weeks (95% CI 8% to 46%).

In the study of Oakland *et al.*⁴ the comparison between ultrasound therapy and Felbinac gel resulted in small and non-significant differences between the two groups at seven days in moderate or marked improvement generally (RR 0.99, 95% CI 0.86 to 1.14; RD -1% 95 CI -13%to 11%), in pain (RR 1.06, 95%CI 0.90 to 1.23; RD 4%95 CI -8%to 17%) and ability to weight bear (RR 1.04, 95% CI 0.86 to 1.26; RD 3%, 95% CI -11% to 17%). Van Lelieveld *et al.*²¹ reported that while ultrasound therapy appeared less beneficial than electrotherapy at seven days, there were no statistically significant differences between the two groups in recovery (pain-free status) (RR 0.83, 95%CI 0.62 to 1.12; RD-15%, 95% CI -38% to 8%); minimal swelling (less than 0.5 cm) (RR 0.76, 95% CI 0.53 to 1.11; RD -20%, 95% CI -46% to 6%) or ability to walk (RR 0.64, 95%CI 0.37 to 1.13; RD-25%, 95%CI -55% to 5%) (Table III).

TABLE III.—*Characteristics of included studies.*

Makuloluwe 1977 ¹	
Methods	Randomised clinical trial (no details of method). No blinding of patients, care providers and outcome assessment
Participants	Enfield, UK 80 patients with ankle sprains Inclusion criteria: mild or moderate ankle sprains, pain on abduction or adduction of the foot Exclusion criteria (X-ray): ankle fractures
Interventions	Group 1: Ultrasound therapy: 1.5 W/cm ² , 4 minutes, 4 to 10 sessions (N.=40). Length of treatment variable depending on recovery Group 2: Immobilisation by Elastoplast (N.=40)
Outcomes	Co-interventions: ice packs for some patients in the ultrasound group Length of follow-up: 2 weeks Success rate / recovery (yes/no) Dropouts: none reported but values of percentages indicate incomplete outcome ascertainment Adverse reactions: not described
Notes	Authors' conclusion: ultrasound is more effective than immobilisation with Elastoplast
Nyanzi 1999 ¹⁹	
Methods	Randomised clinical trial (use of computer generated randomisation scheme). Blinding of patients, care provider, and outcome assessor
Participants	Southampton, UK 58 patients with ankle ligament sprains Inclusion criteria: inversion injury of the joint, time since injury <100 hours, able to follow instructions, age 14 to 65 years. Exclusion criteria: previous similar injury within 1 year, multiple injuries, diabetic, extensive varicose veins, bony injuries. 59% male, 41% female, mean age 50 years
Interventions	Group 1: pulsed ultrasound mark space ratio 1:4, 3 MHz, 0.25 W/cm ² , 2 minutes, 3 treatments over 3 consecutive days (N.=29). Group 2: Sham ultrasound (N.=29) Co-interventions: elevate leg while resting, bear weight when active; Tubigrip support, paracetamol for those in need of analgesics

TABLE III.—*Follows on next page.*

Outcomes	Length of follow-up: 14 days Pain (10 cm VAS, mean and SD) Swelling (ankle joint circumference in cm, mean and SD) ROM dorsiflexion (degrees, mean and SD) ROM plantar flexion (degrees, mean and SD) Ability to bear weight (% bodyweight, mean and SD) Dropouts: N.=7 (12%) (group 1: 3 =10%) and group 2: 4 =14%). All reported full recovery, and had no time to attend further assessments Adverse reactions: not described
Notes	Authors' conclusion: at the dose and duration used, ultrasound is no better than placebo in the management of acute ligament injuries
Oakland 1993 ⁴	
Methods	Randomised clinical trial (use of computer generated randomisation scheme). Blinding of patients. Blinding of care providers and outcome assessment unclear
Participants	Multicentre trial, UK 220 participants with acute ankle injuries Inclusion criteria: injury of the lateral ankle ligament of at least mild severity, time since injury < 48 hours. Exclusion criteria: fractures, internal derangement of the joint, hypersensitivity for felbinac, abraded skin, asthma, metabolic joint diseases or rheumatic conditions, systematic connective tissue disorders, severe renal, hepatic, cardiovascular or dermatological disease, patients requiring analgesics or other NSAID, pregnant or lactating women, participants in other trials 65% men, 35% women, mean age 28 years
Interventions	Group 1: pulsed ultrasound: 3 MHz, 0.25 to 0.5 W/cm ² , 2 to 3 minutes, 4 treatments over 7 days, in combination with felbinac gel: 2-3 applications every day (N.=75). Group 2: sham ultrasound in combination with felbinac gel (N.=72). Group 3: ultrasound in combination with placebo gel (N.=73). Co-interventions: none.
Outcomes	Length of follow-up: 1 week Pain on movement or at rest (yes/no) Moderate or marked response of pain (investigator) (yes/no) Able to bear full weight (yes/no) Moderate or marked improvement of general severity (yes/no) Dropouts: 52 (group 1: 15 = 20%, group 2: 18 = 25%, group 3: 19 = 26%) Adverse reactions (yes/no)
Notes	Authors' conclusions: there were few significant differences between the intervention groups. The effectiveness of felbinac is similar to that of ultrasound therapy
Van Lelieveld 1979 ²¹	
Methods	Randomised clinical trial (computer generated random numbers). Blinding of patients and outcome assessment. No blinding of care provider
Participants	Haslev, Denmark All patients with acute ankle distortions referred to the X-ray department (N.=60) Inclusion criteria: time since injury 0-4 days, first distortion ever 42% men, 58% women, mean age 23 to 29 years
Interventions	Group 1: continuous ultrasound: 0.5 W/cm ² , 5 to 10 minutes, 5x/week, 2 weeks (N.=20?). Group 2: electrotherapy: diadynamic current, pulse duration 10 ms, 50/100 Hz, 4-8 minutes (N.=20?). Group 3: sham ultrasound (N.=20?). Co-interventions: elastic bandages, crutches, leg elevation, plantar flexion exercises
Outcomes	Length of follow-up: 15 days. At baseline, and daily until maximum of 15 days: % patients with swelling <0.5 cm at 7 days % patients able to walk at 7 days % patients pain free at 7 days swelling (joint circumference in cm), means, no SD range of motion (1=20°, 2=40°, 3≥40° restriction), means, no SD pain (6-point scale), means, no SD Dropouts: 3 (2 did not complete treatment; 1 incorrect diagnosis), distribution was not reported Adverse reactions: not described
Notes	Authors' conclusions: ultrasound therapy has no significant effect on the course of recovery. The assumption in the analyses of allocation of 20 patients to each group seems to be supported in the graphical representations

TABLE III.—*Follows on next page.*

Williamson 1986 ²	
Methods	Randomised clinical trial (use of random numbers). Blinding of care provider, patients and outcome assessment
Participants	Manchester, UK All patients with ankle sprains attending the emergency department (n = 154) Inclusion criteria: time since injury < 48 hours, objective injury lateral ankle ligament; age 12 to 65 years Exclusion criteria (X-ray): fractures, complete rupture with > 6mm opening of the ankle mortice laterally or >6 mm anterior displacement of the talus
Interventions	Length of treatment: until recovery (clinical score 0 or 1 point) Group 1: ultrasound on alternate days (74). (Treatment parameters not described.) Group 2: sham ultrasound (80). Co-interventions: ice packs, exercises, Tubigrip support, crutches if needed
Outcomes	Length of follow-up: 4 weeks Follow-up at baseline, at 1 week and 4 weeks: General improvement (scoring system based on clinical score, swelling, patient's discomfort, limp, pain on inversion, and pain on plantar flexion), results presented as percentages in graphs Dropouts: N.=44 (29%) (23 = 31% in the ultrasound group and 21 = 26% in the sham group) after three weeks Adverse reactions: not described
Notes	Authors' conclusions: ultrasound treatment does not hasten recovery after lateral ankle sprains.
Zammit 2005 ²⁴	
Methods	Randomised clinical trial (method?). Blinding patients and no blinding of treatment provider and outcome assessor
Participants	Pietà, Malta All patients with ankle sprains attending the emergency department who met the inclusion and exclusion criteria (N.=34) 14 males,15 females, 5 lost to follow-up, mean age 32 years,17 grade I injury and 12 grade II injury Inclusion criteria: grade 1&2 inversion injuries of the ankle joint, duration since injury: between 24 and 96 hours, age between 20 and 50 years, first distortion ever Exclusion criteria: fractures, complete ruptures (grade III), previous similar injury, multiple injuries, participants in other trials, low back pain with sciatic symptoms, signs of degeneration in lumbar spine, hips and knees, neurological impairment, diabetes, tumors or tissue in precancerous states, infected areas, uncontrollable hemophilia, severely ischemic tissues, recent venous thrombosis, areas of atherosclerosis, areas that have received radiotherapy in the last 6 months, metal bone-fixing pins subcutaneously placed, plastics used in replacement surgery, anesthetic areas
Interventions	Group 1: active ultrasound on alternate days for 2 weeks, ice packs, tubigrip and exercises (N.=12) Group 2: sham ultrasound on alternate days for 2 weeks, ice packs, tubigrip and exercises (N.=10) Group 3: ice packs, tubigrip and exercises (N.=12) Active ultrasound: Treatment sessions were on alternate days for 2 weeks (six sessions); treatment intensity of 0.25 W cm ² at a mark space ratio of 1:4 at 3 MHz was used for the first 3 treatments with duration of 10 min. A treatment intensity of 0.50 W cm ² at a mark space ratio of 1:2 at 3 MHz was used for the last 3 treatments with duration of 6 min
Outcomes	Length of follow-up: 22 days At baseline and after 8, 15 and 22 days: Pain on activity (VAS) scores Swelling (figure-of eight method using a tape measure) Range of motion during dorsiflexion and plantar flexion (universal 360° goniometer) Postural stability (balance error scoring system) Dropouts: 5 (3 after eight days and 2 after 15 days) (group 1: 2 =17%, group 2: 0, group 3: 3 = 25%) Adverse reactions: not described.
Notes	Authors' conclusions: ultrasound treatment does not increase the effectiveness of management of acute lateral ankle ligament sprains.

Discussion

The results of this review show that there is little evidence for beneficial effects of ultrasound therapy for acute ankle sprains. Six trials met the selection criteria. Five placebo-controlled trials could not detect statistically significant or clinically important

differences between true and sham ultrasound for any outcome measure: general improvement, pain, swelling, functional disability or range of motion. The number of studies included in this review was relatively small and only one was of good methodological quality. Due to differences in the definition of outcome measures statistical pooling of re-

sults was only sensible for some comparisons and for most comparisons data from only two or three studies could be used. These pooled estimates also resulted in small and non-significant differences between true and sham ultrasound. Due to the limited amount of information on treatment parameters, no conclusions can be made regarding an optimal and adequate dosage schedule for ultrasound therapy or whether such a schedule would improve on the reported effectiveness of ultrasound for ankle sprains.

One study did detect large and significant differences in favour of ultrasound therapy when compared with immobilisation using Elastoplast.¹ However, this study was considered to be of relatively poor validity and at high risk of bias from lack of blinding. Another pragmatic study comparing ultrasound with electrotherapy reported better results for electrotherapy with respect to improvements of swelling, pain, and ability to walk.²¹ None of the trials included a follow-up period longer than one month. Ultrasound therapy is assumed to be most effective in the first phase of treatment and long-term effects may not be expected.²⁵ Indeed as already stated, the four trials with follow-up periods of two to four weeks showed that the large majority of participants had fully recovered by that time and any differences between intervention groups were negligible.

We prefer to base conclusions regarding the effectiveness of ultrasound therapy on studies with low risk of bias. The Amsterdam- Maastricht Consensus list is one of the many scales and checklists that have been designed to assess the quality of randomised trials.^{15, 16} We added several items from this checklist to The Cochrane Collaboration's 'Risk of bias' tool, as we considered these to be of specific importance in this area of research including control for co-interventions and adherence to treatment. However, very few trials provided information on these aspects of design and conduct. Insufficient reporting of trial methods often hampered the assessment of risk of bias in this review. Journal style or editorial decisions may partly be the reason for the lack of information on important items. A more complete and informative trial report could reveal additional flaws in design or conduct. For example, for none of the trials in this review could we confirm adequate procedures for treatment allocation and adherence to treatment. Insufficient information frequently concerned not only aspects of trial va-

lidity but also diagnostic criteria, details concerning the study populations (athletes or sedentary people), treatment parameters including information on testing and calibration of ultrasound machines, and outcome measures. In this area of research the introduction of guidelines for the reporting of trials (CONSORT statement), does not seem to have led to much improvement in the quality of reporting, which can prevent difficulties during quality assessment and ensure adequate data presentation and analysis.²⁶⁻²⁸

In the six studies included in the review, outcome measures were not uniform and the definitions of general improvement, pain, swelling, and functional disability varied across studies. Some of these measures have probably been designed on the basis of face validity and may have proved useful in clinical practice. Important characteristics of the outcome measures such as reproducibility, validity, responsiveness, or applicability were not described. A thorough assessment of the quality of outcome measures used in the six studies was not feasible within the scope of this review. Lack of blinding was most often considered to be a source of bias, especially in trials without placebo control, or in trials in which the therapist was aware he or she was providing sham ultrasound. Sham ultrasound can be a good placebo, but only if the therapist is adequately blinded.¹¹ Lack of blinding may therefore have resulted in inflated effect sizes in some of the trials. In two trials^{2, 4} there was at least 20% lost to follow-up by the end of the study; this is relatively high in trials with a follow-up period of only one to four weeks.

Our review may not be entirely free from publication bias as we included only published trial reports. However, considering the fact that it is usually small studies with negative results that are less likely to be published,²⁹ we do not think that the inclusion of unpublished data would have strongly influenced the results of our review on the effectiveness of ultrasound therapy for ankle sprains. It must be noted that we identified two Chinese trials published as abstracts only which reported positive results for therapeutic ultrasound.^{30, 31} Both trials included a placebo control but the randomisation procedure was not described at all, making it unclear if these trials used a random procedure to allocate participants to therapeutic ultrasound or the alternative treatment (infrared therapy, Chinese medicine or low dose electrotherapy). In this review we in-

cluded trial reports published in any language. Unfortunately, we were unable to use the same authors for quality assessment of the studies published in English and Danish. The Danish paper was assessed by another author, which may have resulted in a different interpretation of validity criteria.²¹ The findings of the Danish study were not systematically different from those published in English.

In our opinion it is important to consider not only the statistical significance of trial results but also the magnitude of treatment effect. Deciding on the magnitude of a clinically important difference is difficult and certainly arbitrary as it depends on several factors including the natural history, prevalence and severity of the condition, the reference treatment, potential adverse reactions and inconvenience of therapy, treatment preferences, and costs (including costs of personnel, equipment and time spent on therapy).³² Although the definition of a clinically important difference depends on the condition, research in patients with musculoskeletal disorders has shown that differences between study groups may be considered to be clinically important if they exceed 20%.³³ This is a considerable difference that may not be easy to achieve. Given the favourable recovery rates in ankle sprains with most patients showing a full recovery within four weeks, fairly large effect sizes may be needed to have sufficient clinical impact.

Although the quality of methods of most available studies on ultrasound therapy for ankle sprains may be considered to be modest, the findings of the placebo-controlled studies consistently indicated small and non-significant treatment effects of ultrasound therapy. Therefore, future research should preferably be directed towards the evaluation of other interventions for ankle sprains, such as exercise therapy, or to interventions for the prevention of future or recurrent ankle sprains in those who are at a relatively high risk of ankle ligament injuries.³⁴

References

1. Makuloluwe RT, Mouzas GL. Ultrasound in the treatment of sprained ankles. *Practitioner* 1977;218:586-8.
2. Williamson JB, George TK, Simpson DC, Hannah B, Bradbury E. Ultrasound in the treatment of ankle sprains. *Injury* 1986;17:176-8.
3. Karlsson J, Eriksson BI, Sward L. Early functional treatment for acute ligament injuries of the ankle joint. *Scand J Med Sci Sports* 1996;6:341-5.
4. Oakland C, Rapier C. A comparison of the efficacy of the topical NSAID felbinac and ultrasound in the treatment of acute ankle injuries. *British Journal of Clinical Research* 1993;4:89-96.
5. Ebenbichler G, Resch KL. Critical evaluation of ultrasound therapy [Kritische Überprüfung des therapeutischen Ultraschalls]. *Wiener Medizinische Wochenschrift* 1994;144:51-3.
6. Maxwell L. Therapeutic ultrasound: Its effects on the cellular and molecular mechanisms of inflammation and repair. *Physiotherapy* 1992;78:421-6.
7. Hykes DL, Hendrick WR, Starchman DE. Biological effects. *Ultrasound physics and instrumentation*. New York, NY: Churchill Livingstone; 1985. p. 133-47.
8. Falconer J, Hayes KW, Chang RW. Therapeutic ultrasound in the treatment of musculoskeletal conditions. *Arthritis Care Res* 1990;3:85-91.
9. Hayes KW. The use of ultrasound therapy to decrease pain and improve mobility. *Curr Rev Musculoskelet Med* 1992;3:271-87.
10. Kitchen SS, Partridge CJ. A review of therapeutic ultrasound. *Physiotherapy* 1990;76:593-600.
11. van der Heijden GJMG, Bouter LM, Beckerman H, de Bie RA, Oostendorp RAB. De effectiviteit van ultrageluid bij aandoeningen van het bewegingsapparaat: een op methodologische criteria gebaseerde geblijnde review van gerandomiseerd patiëntgebonden onderzoek. *Nederlands Tijdschrift voor Fysiotherapie* 1991;101:169-77.
12. Van den Bekerom MPJ, van der Windt DAWM, van der Heijden GJ, ter Riet G, Bouter LM. Therapeutic ultrasound for acute ankle sprains. *Cochrane Database Syst Rev* 2011;6:CD001250.
13. Van der Windt DAWM, Van der Heijden GJMG, Van den Berg SGM, Ter Riet G, De Winter AF, Bouter LM. Ultrasound therapy for acute ankle sprains. *Cochrane Database of Systematic Reviews* 2002;1.
14. van der Windt DA, van der Heijden GJ, van den Berg SG, ter Riet G, de Winter AF, Bouter LM. Ultrasound therapy for musculoskeletal disorders: a systematic review. *Pain* 1999;81:257-71.
15. Koes BW, Bouter LM, Beckerman H, van der Heijden GJ, Knipschild PG. Physiotherapy exercises and back pain: a blinded review. *BMJ* 1991;302:1572-6.
16. Verhagen AP, de Vet HCW, de Bie RA, Kessels AGH, Boers M, Bouter LM. The Delphi list: a criteria list for quality assessment of randomized clinical trials developed by Delphi consensus. *J Clin Epidemiol* 1998;51:1235-41.
17. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Cont Clin Trials* 1986;7:177-88.
18. Fleiss JL. The statistical basis of meta-analysis. *Stat Methods Med Res* 1993;2:121-45.
19. Nyanzi CS, Langridge J, Heyworth JRC, Mani R. Randomized controlled study of ultrasound therapy in the management of acute ligament sprains of the ankle joint. *Clinical Rehabilitation* 1999;13:16-22.
20. Pellow JE, Brantingham JW. The efficacy of adjusting the ankle in the treatment of subacute and chronic grade I and grade II ankle inversion sprains. *J Manipulative Physiol Ther* 2001;24:17-24.
21. Van Lelieveld DW. The value of ultrasonic and electric stimulation in the treatment of sprained ankles. Report of a controlled investigation [Vaerdien af ultralyd ogel-stimulation ved behandling af distorsioner. En kontrolleret undersøgelse]. *Ugeskrift for Laeger* 1979;141:1077-80.
22. Bradnock B, Law HT. Assessment of different ultrasonic devices in the treatment of acute ankle sprains using gaitway, gait analysis [abstract]. *J Bone Joint Surg Am* 1994;76(Suppl 2 & 3):142.
23. Middlemast S, Chatterjee DS. Comparison of ultrasound and thermotherapy for soft-tissue injuries. *Physiotherapy* 1978;64:331-2.
24. Zammit E, Herrington L. Ultrasound therapy in the management of acute lateral ligament sprains of the ankle joint. *Physical Therapy in Sport* 2005;6:116-21.

- for preventing ankle ligament injuries. Cochrane Database of Systematic Reviews 2002;1.

Funding.—The authors did receive funding from VU University Medical Center, Amsterdam, Netherlands and from Fund for Investigative Medicine, Health Insurance Council, Netherlands in support of their research for or preparation of this work.

Acknowledgments.—The authors gratefully acknowledge the help of Wim Grooten in evaluating the study published in Danish and the help of Vicky Peng in translating the Chinese abstracts. We are grateful to Helen Handoll for her help with editing both the protocol and several versions of the review. For the later updates we are grateful to Lesley Gillespie, Lindsey Elstub, and Joanne Elliott for updating the searches, and to Janet Wale for copy-editing as part of the Wiley copy-editing support project. We would also like to thank the following for useful editorial comments of both the protocol and review: Prof William Gillespie, Dr Helen Handoll, A/Prof Peter Herbison, Ms Denise Jones, Prof Rajan Madhok, Prof Gordon, Dr Sally Rudicel, Prof Marc Swiontkowski, and Mr Stephen Wrigley. We acknowledge the contributions of Suzanne van den Berg and Andrea de Winter to earlier versions of this review.