Hyperbaric oxygen therapy for chronic wounds (Review)

Kranke P, Bennett MH, Martyn-St James M, Schnabel A, Debus SE, Weibel S

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[Intervention Review]

Hyperbaric oxygen therapy for chronic wounds

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ABSTRACT

Background

Chronic wounds are common and present a health problem with significant effect on quality of life. Various pathologies may cause tissue breakdown, including poor blood supply resulting in inadequate oxygenation of the wound bed. Hyperbaric oxygen therapy (HBOT) has been suggested to improve oxygen supply to wounds and therefore improve their healing.

Objectives

To assess the benefits and harms of adjunctive HBOT for treating chronic ulcers of the lower limb.

Search methods

For this second update we searched the Cochrane Wounds Group Specialised Register (searched 18 February 2015); the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2015, Issue 1); Ovid MEDLINE (1946 to 17 February 2015); Ovid MEDLINE (In-Process & Other Non-Indexed Citations, 17 February 2015); Ovid EMBASE (1974 to 17 February 2015); and EBSCO CINAHL (1982 to 17 February 2015).

Selection criteria

Randomised controlled trials (RCTs) comparing the effect on chronic wound healing of therapeutic regimens which include HBOT with those that exclude HBOT (with or without sham therapy).

Data collection and analysis

Three review authors independently evaluated the risk of bias of the relevant trials using the Cochrane methodology and extracted the data from the included trials. We resolved any disagreement by discussion.

Main results

We included twelve trials (577 participants). Ten trials (531 participants) enrolled people with a diabetic foot ulcer: pooled data of five trials with 205 participants showed an increase in the rate of ulcer healing (risk ratio (RR) 2.35, 95% confidence interval (CI) 1.19 to 4.62; P = 0.01) with HBOT at six weeks but this benefit was not evident at longer-term follow-up at one year. There was no statistically significant difference in major amputation rate (pooled data of five trials with 312 participants, RR 0.36, 95% CI 0.11 to

1.18). One trial (16 participants) considered venous ulcers and reported data at six weeks (wound size reduction) and 18 weeks (wound size reduction and number of ulcers healed) and suggested a significant benefit of HBOT in terms of reduction in ulcer area only at six weeks (mean difference (MD) 33.00%, 95% CI 18.97 to 47.03, P < 0.00001). We identified one trial (30 participants) which enrolled patients with non-healing diabetic ulcers as well as venous ulcers ("mixed ulcers types") and patients were treated for 30 days. For this "mixed ulcers" there was a significant benefit of HBOT in terms of reduction in ulcer area at the end of treatment (30 days) (MD 61.88%, 95% CI 41.91 to 81.85, P < 0.00001). We did not identify any trials that considered arterial and pressure ulcers.

Authors' conclusions

In people with foot ulcers due to diabetes, HBOT significantly improved the ulcers healed in the short term but not the long term and the trials had various flaws in design and/or reporting that means we are not confident in the results. More trials are needed to properly evaluate HBOT in people with chronic wounds; these trials must be adequately powered and designed to minimise all kinds of bias.

PLAIN LANGUAGE SUMMARY

Hyperbaric oxygen therapy for treating chronic wounds

Background

Chronic wounds are wounds that take a long time to heal, do not heal, or recur; these wounds are often ulcers associated with diabetes or arterial or venous disease (poor blood circulation). One characteristic of chronic wounds is that the wound tissues are hypoxic (have low oxygen levels). Chronic wounds are commonly occurring and reduce the quality of life of those affected.

Hyperbaric oxygen therapy (HBOT) is a treatment designed to increase the supply of oxygen to wounds that are not responding to other treatments. HBOT involves people breathing pure oxygen in a specially designed compression chamber (such as those used for deep-sea divers suffering pressure problems after resurfacing).

Review question

Does hyperbaric oxygen therapy (HBOT) increase the rate of healing of people with chronic wounds and reduce the need for partial or total lower limb amputation? Is this treatment safe?

What we found

We included twelve randomised trials (577 participants) in this updated review. Most of the included trials studied foot ulcers in people with diabetes (10 trials).

For diabetes-related foot ulcers, we found that HBOT seemed to improve the chance of healing in the short term (up to six weeks), but not with longer term follow-up. HBOT may reduce the number of major amputations in people with diabetes who have chronic foot ulcers.

For chronic wounds caused by disease to the veins of the leg, we found that HBOT may reduce the size of wounds.

For chronic wounds caused by lack of blood supply through the arteries or chronic pressure ulcers, we found no evidence to confirm or refute any effects of HBOT.

We could not assess safety as none of the trials included in our review reported whether there were any major adverse events.

This plain language summary is up-to-date as of 23/1/15

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Hyperbaric Oxygen Therapy for chronic wounds

Patient or population: patients with chronic wounds
Settings: inpatients and outpatients in a hyperbaric facility
Intervention: Hyperbaric Oxygen Therapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Hyperbaric Oxygen Therapy				
Diabetic ulcers healed at 1 year. Follow-up: 1 years	**Study population**		**RR 9.53** (0.44 to 207.76)	212 (3 studies)	⊕⊕⊕◯ **moderate**[1,2,3]	
	115 per 1000	**1000 per 1000** (51 to 1000)				
	Low					
	0 per 1000	**0 per 1000** (0 to 0)				
	High					
	0 per 1000	**0 per 1000** (0 to 0)				
Diabetic ulcers - major amputations	**Study population**		**RR 0.36** (0.11 to 1.18)	312 (5 studies)	⊕⊕⊕◯ **moderate**[2]	
	247 per 1000	**89 per 1000** (27 to 284)				
	Low					

	0 per 1000	**0 per 1000** (0 to 0)	
	High		
	0 per 1000	**0 per 1000** (0 to 0)	

*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] Analysis comprises small studies, some with zero events in control arm
[2] small sample size
[3] very large effect: RR >5

BACKGROUND

Description of the condition

A chronic wound is any interruption in the continuity of the body's surface that requires a prolonged time to heal, does not heal, or recurs (Wysocki 1996). For the purpose of this review we have generally defined 'chronic' as those wounds where attempts to heal by means other than hyperbaric oxygen therapy have failed. Chronic wounds arise in a great variety of situations and may be associated with a number of pathological processes. In order to institute appropriate therapy, it is common practice to define such wounds by their most likely aetiology. Thus, wounds developing in the presence of demonstrated arterial insufficiency would be termed 'arterial ulcers' and therapeutic measures would aim to improve ischaemia in the limb in order to promote healing, perhaps through bypass surgery when technically possible (Fowkes 2008). In ulcers associated with venous insufficiency, on the other hand, compression bandaging is likely to be more appropriate (O'Meara 2009; Escaleira 2010). The most common chronic wounds encountered in western medical practice are a consequence of diabetes, arterial and/or venous disease, sustained pressure, and those as a result of therapeutic irradiation for the treatment of tumours. More than one such process may be present in an individual and contribute to the wound and they are more common in the elderly and those with multiple health problems (Dealey 1994; Lauterbach 2010). Chronic wounds are common and constitute a significant health problem. The true incidence and impact are difficult to assess accurately given the wide range of disease, the fact that much care is delivered at home and that many wound care products are purchased directly in some countries. While most leg ulcers will be the result of venous insufficiency, about 25% are likely to be arterial (Andersson 1993; O'Meara 2009). Wound care in the UK costs in excess of GBP 1 billion per year and therefore treatment options that are both clinically effective and cost-effective are vital (Banwell 1999). The availability of a great variety of treatment options for chronic wounds is a consequence of the range of different aetiologies. However, there is also a possibility that many of the treatment options are ineffective. By definition, chronic wounds are indolent or progressive and resistant to the wide array of treatments applied. There is a plethora of wound care products available - many at considerable cost. In some areas, dedicated wound care teams have been developed in an attempt to maximise successful healing and contain costs through improved efficiency.

Wound management techniques are continuously being developed. Strategies include treatment of the underlying pathology (e.g. optimal diabetes care with blood glucose control, vein surgery, arterial reconstruction), systemic treatment aimed at improving the local wound environment (e.g. nutrition supplements, pentoxifylline, aspirin, flavonoids, thromboxane alpha-2 agonists, sulodexide) (Langer 2003; Palfreyman 2006; Jull 2007) and local treatment aimed at improving the wound environment (e.g. dressings, negative local pressure, pressure-relieving mattresses, ultrasound, application of growth factors, skin-grafting) (Jull 2008; Ubbink 2008; Akbari Sari 2009; Jones 2009; Cullum 2010; Edwards 2010; Aziz 2011; Dumville 2011a; Dumville 2011b). There are many others. In practice, wound management is often a sequential search for a successful combined approach.

Wound types

Diabetic foot ulcer

One particular type of chronic wound often associated with ischaemia is the foot ulcer associated with diabetes. It has been estimated that 2% of the UK population have diabetes, of whom up to 25% experience foot ulceration and in whom the amputation rate is 15 to 70 times that in the general population (SIGN 1997; Calman 1998; Singh 2005). In diabetes mellitus, the development of foot ulcers is usually the result of peripheral neuropathy and/or peripheral vascular disease. The annual incidence of foot ulcers among people with diabetes has been variously estimated a between 2.5% to 10.7%, and the annual incidence of amputation is 0.25% to 1.8% (Apelqvist 1993; Lee 1993; Humphrey 1996; Boulton 2008). Ulcer care is responsible for a large proportion of the cost of health care for people with diabetes. The relapse rate for diabetic foot ulcers is 66% over five years. Approximately 12% of people with ulcers progress to lower extremity amputation (Apelqvist 1993).

Venous ulcer

Venous ulcers (also known as varicose or stasis ulcers) are caused by venous reflux or obstruction resulting in high venous pressure. Estimates for the prevalence of leg ulcers range between 1.5 and 3 per 1000 population, and 1% to 2% of people will have a venous ulcer at least once during their life (Amsler 2009). The rate increases with age to about 20 per 1000 people aged over 80 years (Callam 1985). It has been estimated that in the UK, the cost to the NHS of treatment for venous ulcers alone may be GBP 300 to 450 million annually (Bosanquet 1992), and that district nurses devote between 25% and 50% of their time to the care of people with ulcers (Lees 1992).

Arterial ulcer

Arterial ulcers are the result of impaired perfusion to the feet or legs and are viewed as one clinical sign of general arteriosclerosis. Intermittent claudication may accompany this disease and can be usually found at earlier stages of the arteriosclerosis, while skin lesions or even necrosis represent an end stage of the peripheral manifestation of general arteriosclerosis.

Pressure ulcer

Pressure ulcers (also known as pressure sores, decubitus ulcers and bed sores) may present as broken or necrotic skin, most often extending to the underlying tissue, including muscles and bone. They are caused by unrelieved pressure or friction and can be found predominantly below the waist and at bony prominences (sacrum, heels, hips). Increased age, reduced mobility and malnutrition constitute relevant risk factors, however, their respective impact on the genesis of ulcers remains unknown (Allman 1997; Reddy 2008). Pressure ulcers can be viewed as typical complications in all healthcare settings with a prevalence of 6% to 10% in National Health Services hospitals in the UK (O'Dea 1999)

Description of the intervention

Hyperbaric oxygen therapy (HBOT) is a treatment modality that has been used in chronic wounds for about 40 years (Kulonen 1968). It is relatively widely available in North America (where there are more than 300 facilities registered with the Undersea and Hyperbaric Medical Society (UHMS)), Russia, China and Cuba, but less well-established in Europe and Australasia (UHMS 2001a). Treatment involves placing the patient in a compression chamber, increasing the environmental pressure within the chamber, and administering 100% oxygen for respiration. In this way, it is possible to deliver a greatly increased partial pressure of oxygen to the tissues. Typically, treatments involve pressurisation to between 2.0 and 2.5 atmospheres absolute (ATA) for periods between 60 and 120 minutes once or twice daily. A typical course might involve 15 to 30 such treatments.

How the intervention might work

The rationale for HBOT is that, despite the wide range of causative pathologies, the common denominator in many wounds is tissue hypoxia. Wound healing is a complex and incompletely understood process. While it appears that in acute wounds healing is enabled by the initial hypoxia, low pH and high lactate concentrations found in freshly injured tissue (Knighton 1983; Jensen 1986), some elements of tissue repair are extremely oxygen-dependent, for example collagen elaboration and deposition by fibroblasts (Hunt 1972; Niinikoski 1972a) and bacterial killing by macrophages (Hohn 1976). In a complicated balance between wound hypoxia and peri-wound oxygenation, it would seem that successful healing relies on adequate tissue oxygenation in the area surrounding the fresh wound. Certainly, wounds that lie in hypoxic tissue beds are those that most often display poor or absent healing (Niinikoski 1972b; Sheffield 1985).

Some causes of tissue hypoxia will be reversible with HBOT, while some will not. One very common cause for peripheral tissue hypoxia is ischaemia due to large vessel disease. In this situation, although the administration of HBOT will result in very high arterial partial pressures of oxygen, this oxygen will not reach the wound bed due to inadequate perfusion. In other clinical situations the cause of tissue hypoxia may be small vessel disease or oedema, and may be overcome by a high driving pressure of oxygen in the arterial blood. This has been demonstrated in hypoxic tissues where regional perfusion is reasonably preserved, through the use of transcutaneous and implantable oxygen electrodes (Sheffield 1985). In wound healing, insufficient supply of oxygen may prevent normal healing processes. The intermittent presentation of oxygen to those hypoxic tissues, therefore, may allow a resumption of normal healing. HBOT administration in man has been demonstrated to cause hyper-oxygenation of tissue, vasoconstriction, fibroblast activation, down-regulation of inflammatory cytokines, up-regulation of growth factors, antibacterial effects, potentiation of antibiotics, and a reduction in leukocyte chemotaxis (Sheffield 1985; Rabkin 1988; Cianci 1993; Stevens 1993; Zhao 1994; Bayati 1998; Dimitrijevich 1999).

Oxygen in high doses is toxic to normally perfused tissue, in particular the brain and lungs. Therefore it is not possible to expose patients to typical wound treatment pressures for longer than one to two hours on a regular basis and the question arises as to how such short exposures could be expected to result in a clinical benefit. There are two principal reasons why this might be so. First, elevation of wound oxygen tension may persist for some hours following HBOT and so exert therapeutic effects for rather longer than might be expected (Siddiqui 1997). Second, there is experimental evidence that repeated 'on-off' exposures do produce an environment favourable to healing when compared to oxygen or air at normobaric pressure. In a rabbit model where wounds were produced by irradiation to the lower face, Marx 1990 assessed the angiogenic properties of normobaric oxygen (100% oxygen at 1 ATA for 90 minutes daily) and hyperbaric oxygen (100% oxygen at 2.4 ATA for 90 minutes daily for 20 days), as compared with air-breathing controls. Results indicated that normobaric oxygen had no angiogenic properties above the normal revascularisation of irradiated tissue than air-breathing controls (P = 0.89). Hyperbaric oxygen demonstrated an eight- to nine-fold increased vascular density over both normobaric oxygen and air-breathing controls (P = 0.001).

Why it is important to do this review

HBOT is always presented as an adjunctive therapy to normal wound care measures, and is not proposed as an alternative therapy capable of inducing healing in the absence of good wound care (UHMS 2001). Using both clinical assessment and investigations designed to confirm significant peri-wound hypoxia, hyperbaric practitioners attempt to select those wounds where a response to HBOT is considered likely. Often this decision is based on transcutaneous oxygen measurements of the peri-wound area, both while air-breathing at normal pressure and on administration of hyperbaric oxygen. If HBOT can be shown to have a beneficial

effect on wound healing, then we hypothesise that the addition of this treatment modality may improve the proportion of wounds that achieve healing and thereby enhance the quality of life in such selected participants. One review suggests the addition of HBOT may reduce the overall costs associated with the treatment of diabetic ulcers (Chuck 2008).

HBOT is associated with some risk of adverse effects including damage to the ears, sinuses and lungs from the effects of pressure, temporary worsening of short-sightedness, claustrophobia and oxygen poisoning (Clarke 2003). Although serious adverse events are rare, HBOT cannot be regarded as an entirely benign intervention. Furthermore, as an adjunct to standard therapy HBOT may be associated with increased costs, and any cost/benefit advantage should be carefully assessed. The administration of HBOT for people with chronic wounds remains controversial. While much of the justification derives from pathophysiology and anecdote, there have been a number of attempts to demonstrate a beneficial effect in formal clinical trials in a variety of disease states. In this review we have limited our interest to those chronic wounds associated with diabetes mellitus, peripheral arterial and venous disease and pressure-related ulcers. The treatment of wounds related to therapeutic irradiation will be the subject of a separate review.

OBJECTIVES

The aim of this review was to assess the evidence for the benefit of hyperbaric oxygen treatment (HBOT) for the treatment of chronic wounds. Does HBOT:

- increase the rate of healing of diabetic foot ulcers?
- increase the rate of healing of venous leg ulcers?
- increase the rate of healing of arterial ulcers of the lower limb?
- increase the rate of healing of pressure ulcers?
- reduce the proportion of people with diabetic foot ulcers who undergo partial or total amputation of the lower limb?
- reduce the proportion of people with arterial ulcers of the lower limb who undergo partial or total amputation of the lower limb?

Is HBOT safe in the short and long term?

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) that compare the effect on chronic wound healing of treatment with HBOT compared with no HBOT.

Types of participants

Any person in any healthcare setting with a chronic wound associated with venous or arterial disease, diabetes mellitus or external pressure. We defined chronic wounds as described in the retrieved papers (prolonged healing or healing by secondary intention), but there must have been some attempt at treatment by other means prior to the application of HBOT.

Types of interventions

Wound care regimens which included HBOT compared with similar regimens that excluded HBOT. Where co-interventions differed significantly between trials we clearly stated this and discussed the implications.

HBOT administered in a compression chamber between pressures of 1.5 ATA and 3.0 ATA and treatment times between 30 minutes and 120 minutes daily or twice daily. The comparator group was diverse; we accepted any standard treatment regimen designed to promote wound healing. The salient feature of the comparison group was that these measures had failed before enrolment in the trials. We planned subgroup analysis to evaluate the impact of different comparator strategies.

Types of outcome measures

Primary outcomes

Diabetic ulcers:
- proportion of ulcers healed;
- proportion of people undergoing major amputation

(defined as amputation of the lower or upper extremity above the ankle or the wrist, respectively).

Venous ulcers:
- proportion of ulcers healed.

Pressure ulcers:
- proportion of ulcers healed.

Mixed ulcers group:
- proportion of ulcers healed.
- proportion of people undergoing major amputation

(defined as amputation of the lower or upper extremity above the ankle or the wrist, respectively).

Secondary outcomes

Diabetic ulcers:
- time to complete healing;
- wound size reduction;
- proportion undergoing minor amputation (defined as amputation of a hand or foot or any parts of either);
- quality of life;
- transcutaneous oxygen tensions and recurrence rate.

Venous ulcers:
- time to complete healing;
- wound size reduction;
- quality of life;
- pain;
- recurrence rate.

Pressure ulcers:
- time to complete healing;
- wound size reduction;
- quality of life;
- recurrence rate.

Mixed ulcers group:
- time to complete healing;
- wound size reduction;
- proportion undergoing minor amputation (defined as amputation of a hand or foot or any parts of either);
- quality of life;
- transcutaneous oxygen tensions and recurrence rate.

Adverse events of HBOT:
- proportion of people with visual disturbance (short and long-term);
- barotrauma (aural, sinus, pulmonary in the short and long-term);
- oxygen toxicity (short-term) with respect to HBOT obtained from the included trials;
- any other adverse events.

We also examined the proportion of people withdrawn from treatment for any reason and planned to relate such withdrawals to the frequency and dose of HBOT where possible.

Search methods for identification of studies

The search methods section of the original version of this review can be found in Appendix 1.

Electronic searches

For this second update we searched the following electronic databases:
- The Cochrane Wounds Group Specialised Register (searched 18 February 2015);
- The Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2015, Issue 1);
- Ovid MEDLINE (1946 to 17 February 2015);
- Ovid MEDLINE (In-Process & Other Non-Indexed Citations, 17 February 2015);
- Ovid EMBASE (1974 to 17 February 2015);
- EBSCO CINAHL (1982 to 17 February 2015).

We used the following search strategy in the Cochrane Central Register of Controlled Trials (CENTRAL):
#1 MeSH descriptor: [Chronic Disease] explode all trees 10595
#2 MeSH descriptor: [Wound Healing] explode all trees 4098
#3 #1 and #2 280
#4 MeSH descriptor: [Skin Ulcer] explode all trees 1720
#5 MeSH descriptor: [Diabetic Foot] explode all trees 433
#6 (skin next ulcer*) or (foot next ulcer*) or (diabetic next (foot or feet)) or (leg next ulcer*) or (varicose next ulcer*) or (venous next ulcer*) or (stasis next ulcer*) or (arterial next ulcer*) 2790
#7 ((ischaemic or ischemic) next (wound* or ulcer*)) 88
#8 (bed next sore*) or (pressure next sore*) or (pressure next ulcer*) or (decubitus next ulcer*) 1174
#9 (chronic next wound*) 292
#10 (chronic near ulcer*) 1099
#11 #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 4559
#12 MeSH descriptor: [Hyperbaric Oxygenation] explode all trees 358
#13 hyperbar* next oxygen* 751
#14 high next pressure next oxygen* 18
#15 oxygen*:ti 4393
#16 #12 or #13 or #14 or #15 4549
#17 #11 and #16 113

The search strategies for Ovid MEDLINE, Ovid EMBASE and EBSCO CINAHL can be found in Appendix 2; Appendix 3 and Appendix 4 respectively. We combined the Ovid MEDLINE search with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximising version (2008 revision) (Lefebvre 2011). We combined the Ovid EMBASE and EBSCO CINAHL searches with the trial filters developed by the Scottish Intercollegiate Guidelines Network (SIGN) (SIGN 2011). There were no restrictions with respect to language, date of publication or trial setting. We contacted authors to discuss any ambiguity about the published data.

Searching other resources

We searched the bibliographies of all retrieved and relevant publications to identify any further eligible trials.

Data collection and analysis

Selection of studies

For the original version of the review, one review author (MB) was responsible for handsearching and identifying appropriate trials for consideration. Three review authors (PK, MB and IR) independently examined the electronic search results and identified potentially relevant trials. We retrieved all comparative clinical trials identified and judged to be potentially relevant in full and three review authors reviewed them independently, two with content expertise in the treatment of chronic wounds with HBOT, one with content expertise in treating chronic wounds without HBOT. In addition, two of the review authors (MB, IR) have expertise in clinical epidemiology. For the review update, four review authors made trial selection decisions (SW, MB, MMSJ, and AS).

Data extraction and management

Using the data extraction form developed for this review, each review author extracted relevant data and made a recommendation for inclusion or exclusion in this review based on an appraisal of the trial methodology. The number of participants originally allocated to the HBOT and control groups was extracted to allow an 'intention-to-treat analysis' (ITT) approach in the meta-analysis (see Dealing with missing data and Data synthesis). We identified losses to follow-up where this information was reported.

For the update, MB and SW undertook data extraction and this was checked by PK. We settled any differences by consensus. The data extracted included the following.

1. Trial authors
2. Year of publication
3. Study design (RCT)
4. Inclusion criteria for participants
5. Baseline characteristics of participants
6. Numbers recruited and allocated
7. Method of randomisation
8. Method of participant allocation
9. Blinding of participants and trial personnel
10. Details of the intervention (treatment and comparator)
11. Setting of treatment
12. Duration of intervention/follow-up periods
13. Outcomes measured
14. Number of participants completing
15. Reporting of withdrawals
16. Reasons for participant withdrawal
17. Statistical methods used in the analysis
18. Methods for handling missing data (per-protocol or ITT analysis)
19. Results per group for each outcome
20. Adverse events

Assessment of risk of bias in included studies

We appraised each included trial to assess the risk of bias as outlined in section 8.5 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and according to the criteria described below. 'Unclear risk' means that insufficient information was available to make a judgement.

1. Random sequence generation (selection bias)

Low risk: adequate sequence generation was reported using random number tables, computer random number generator, coin tossing or card/envelope shuffling.

High risk: used a system involving dates, names or admittance numbers for the allocation of participants. We considered such trials as quasi-randomised and excluded them from the review.

Unclear risk: did not describe one of the adequate methods but mentioned randomisation.

2. Allocation concealment (selection bias)

Low risk: a randomisation method was described that would not allow an investigator/participant to know or influence allocation to an intervention group before an eligible participant entered the trial, such as central randomisation or serially numbered, opaque, sealed envelopes.

High risk: an inadequate method of allocation was used, such as alternate medical record numbers or unsealed envelopes; or there was information in the trial report indicating that investigators or participants could have influenced group allocation.

Unclear risk: the trial report mentioned randomisation but there was no information on the method used, or a method was reported that was not clearly adequate.

3. Blinding of participants (performance bias and detection bias)

We graded this item as 'low risk' for blinding participants, 'unclear' if the relevant information was not stated in the trial report and 'high risk' for unblinded participants.

4. Blinding of outcome assessors (performance bias and detection bias)

We graded this item as 'low risk' for blinded outcome assessment, 'unclear' if the relevant information was not stated in the trial report and 'high risk' for any statement indicating unblinded outcome assessment.

5. Incomplete outcome data addressed (description of withdrawals)

Low risk: numbers of withdrawals per group with reasons provided; or clear from report that there were no withdrawals.

High risk: some withdrawal evident but numbers per group and reasons not provided.

Unclear risk: unclear from trial report whether there were any withdrawals.

6. Incomplete outcome data addressed (use of intention-to-treat (ITT) analysis)

We defined ITT analysis as being conducted when all trial participants were analysed in the group to which they were randomised regardless of which (or how much) of the treatment they actually received, and regardless of other protocol irregularities, such as ineligibility.

Low risk: trial report stated that ITT was undertaken and this was confirmed on trial assessment, or not stated but evident from trial assessment that ITT was undertaken.

High risk: ITT not confirmed on trial assessment (participants who were randomised were not included in the analysis because they did not receive the trial intervention, they withdrew from the trial or were not included because of protocol violation) regardless of whether analysis described as ITT.

Unclear risk: described as ITT analysis, but unable to confirm on trial assessment, or not reported and unable to confirm by trial assessment.

7. Selective reporting

We defined selective reporting as whether all outcomes detailed in an original trial protocol were presented in the published report as follows:

Low risk: all outcomes in trial protocol are reported.

High risk: only certain outcomes from the original protocol (for example outcomes with a statistically significant beneficial effect) are reported

Unclear risk: full trial protocol not available (from trial investigators or a trials register).

In the absence of the availability of a full trial protocol for any included report, we noted whether the results section of the published report presented results for all outcomes that were described in the methods section.

Measures of treatment effect

Dichotomous data

For the dichotomous outcomes we presented the summary estimate as a risk ratio (RR) with 95% confidence intervals (CI). We estimated the RR using the intention-to-treat (ITT) data of the treatment group (HBOT) compared with the ITT of the control group. The dichotomous outcomes included the following.

1. Wounds healed
2. Major amputations
3. Minor amputations
4. Ulcer recurrence
5. Adverse events

In the original review we presented a RR of failing to heal. For this update, we presented the RR of healing in order to facilitate ease of interpretation for the reader of the healing outcomes. The interpretation of the RR was that a summary estimate in which HBOT increased the occurrence of healing would have a RR > 1.00 and a summary estimate in which HBOT reduced the occurrence of amputation, ulcer recurrence or adverse events would have a RR < 1.00.

For the dichotomous outcomes, we analysed the number of reported events in each arm against the number of participants originally randomised to that arm at trial enrolment (ITT). We then undertook sensitivity analyses to include people (events) potentially lost to follow-up (see Dealing with missing data).

Continuous data

Where continuous outcomes were measured in the same way across trials, we presented a mean difference (MD) with 95% CI. We presented a standardised mean difference (SMD) where trials measured the same outcome using different methods. The continuous outcomes included the following.

1. Time to complete healing
2. Ulcer size reduction
3. Quality of life
4. Transcutaneous oxygen tension
5. Pain

Dealing with missing data

For the trials indicating missing data as participants allocated for whom no outcome data were presented, we adopted the 'best-case' and 'worst-case' scenario method cited in section 16.2 in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). The 'best-case' scenario is that all participants with missing outcomes in the experimental intervention group had good outcomes, and all those with missing outcomes in the control intervention group had poor outcomes. The 'worst-case' scenario is the converse.

Data synthesis

We undertook statistical pooling using Cochrane RevMan software (version 5.3) (RevMan 2014). We assessed statistical between-trial heterogeneity using the I^2 statistic (Higgins 2011). We applied a fixed-effect model where trials examined the same interventions, the populations and methods described were sufficiently similar, and low levels of between-trial heterogeneity were evident ($I^2 \leq 30\%$, Higgins 2011). If statistical heterogeneity was detected, we used a random-effects model to produce an overall summary estimate. As an estimate of the clinical relevance of any difference between experimental intervention and control intervention we calculated the number needed to treat (NNT) with 95% CI as appropriate. We undertook and presented a narrative synthesis of all trials.

Subgroup analysis and investigation of heterogeneity

Since the obtained NNTs or numbers needed to harm (NNHs) differ depending on the underlying risk for an event in the trial population, we considered subgroup analyses due to different baseline risks, in which case we planned to use 'truncated' data restricting the analyses to a predefined control event rate.

Where appropriate data were available, we also considered subgroup analysis based on the following.

1. Wound entry grade or severity using established wound classification systems where the authors have employed those systems.
2. Dose of oxygen received (pressure, time and length of treatment course).
3. Nature of the comparative treatment modalities.

Sensitivity analysis

We undertook sensitivity analysis for the effects of missing data, employing the best-case and worse-case scenarios as described above.

RESULTS

Description of studies

Results of the search

In our original report, we identified 26 publications dealing with the treatment of chronic wounds with adjunctive HBOT and for the first update we identified a further 25 publications, for the second update we identified a further 24 publications. Initial examination suggested 31 possible comparative trials where systemic hyperbaric oxygen was employed in at least one arm of the trial. After appraisal of the full report for these trials, we excluded 18 publications. Twelve trials met the inclusion criteria for the review. We identified two published protocols to ongoing trials and added those to Characteristics of ongoing studies for consideration in a subsequent update (O'Reilly 2011; Stoekenbroek 2015).

Included studies

In total, twelve trials contributed to this review and these were published between 1992 (Doctor 1992) and 2014 (Ma 2013). In total, these trials include data on 577 participants, 281 receiving HBOT and 267 receiving control or comparator treatment, and the largest (Duzgun 2008) accounts for 17% of participants. In the reports of Doctor 1992 and Lin 2001, the number of participants randomised to each arm was not specified, and we were unable to obtain this information through contact with the authors. We have assumed an equal distribution for this review. One of the trials included patients with venous ulcers (Hammarlund 1994), and one trial included a mixed group of patients with diabetic and venous ulcers (Kaur 2012), while the other ten included people with diabetic ulcers (See Characteristics of included studies).

Diabetic foot ulcers

Ten trials comparing HBOT with control (either with or without sham) enrolling a total of 531 people with diabetic ulcers were included in this analysis (Abidia 2003; Doctor 1992; Duzgun 2008; Faglia 1996a; Kessler 2003; Lin 2001; Londahl 2010; Khandelwal 2013; Ma 2013; Wang 2011). The treatment pressure and time schedule used for delivery of oxygen varied between trials. Doctor 1992 used 3.0 ATA for 45 minutes, while the remainder used between 2.2 and 2.5 ATA for between 60 and 120 minutes. Nine trials gave between 20 and 40 sessions once or twice daily either five or six days each week, whilst one trial (Doctor 1992) unusually applied four sessions only, over a period of two weeks. Three trials (Abidia 2003; Lin 2001; Londahl 2010) employed a sham treatment in the control group, on the same schedule as the HBOT group. The other seven trials did not employ a sham therapy (Doctor 1992; Faglia 1996a; Kessler 2003; Duzgun 2008; Khandelwal 2013; Ma 2013; Wang 2011).

Inclusion criteria varied in these trials. Doctor 1992 included any person with diabetes with a chronic foot lesion (time not specified); Faglia 1996a included people with diabetes and Wagner grade 2, 3 or 4 lesions (Wagner 1987); Lin 2001 and Kessler 2003 people with "early diabetic feet", Wagner grades 0, 1 or 2, while Duzgun 2008; Abidia 2003 and Londahl 2010 included people with diabetes whose lesions had been present for more than four weeks, six weeks and three months respectively. In addition, Londahl 2010 required evidence of good standard wound care in a specialist clinic setting for a minimum of two months. Exclusion criteria generally followed from the specific inclusions detailed above, but Abidia 2003 also specifically excluded participants for whom vascular surgical procedures were planned and Kessler 2003 excluded all patients with transcutaneous oxygen tensions of < 30 mmHg. Ma 2013 included patients with diagnosed diabetes, at least one full-thickness wound below the ankle (Wagner grades III or less) for > 3 month, standard care for > 2 month, TcPO2 > 30 mmHg. Khandelwal 2013 included patients with a diabetic foot ulcer of at least 8 weeks duration, patients with only stage III and IV diabetic foot ulcer and the absence of vascular insufficiency.

Overall sample size ranged from 18 participants (Abidia 2003) to 100 participants (Duzgun 2008). Only one trial reported undertaking a sample size calculation, which was for amputation rate (34 in each arm, Faglia 1996a). There is a possibility that some of the included trials may have been underpowered to detect a statistically significant effect of HBOT on healing or amputation rates. Where baseline ulcer size and duration were reported (Abidia 2003; Kessler 2003; Londahl 2010), there were no between-group imbalances evident from the published report.

Given the different centres involved, the comparator treatment was unlikely to have been exactly the same in any of the trials. One trial did not specify any comparator (Lin 2001). Sixtrials described a comprehensive and specialised multidisciplinary wound management programme to which HBOT was added for the active arm of the trial (Faglia 1996a; Abidia 2003; Kessler 2003; Duzgun 2008; Londahl 2010; Ma 2013), and one specified a surgical and dressing regimen common to both arms (Doctor 1992).

The follow-up periods varied between trials. Two trials reported data immediately following the course of therapy (Lin 2001; Ma 2013), two trials followed patients to discharge from hospital (Doctor 1992; Faglia 1996a), one followed patients for two weeks after therapy (Kessler 2003), one followed patients for ten weeks or till the ulcers healed (Khandelwal 2013), two gave results at one year (Abidia 2003; Londahl 2010) and one trial followed patients for 22 months (Duzgun 2008). All included trials reported at least one outcome of interest. Other outcomes reported included positive wound cultures (Doctor 1992), number of outpatient visits and cost of wound dressings over one year (Abidia 2003), vascular responsiveness (Abidia 2003), transcutaneous oximetry (Kessler 2003) and laser-Doppler perfusion scans (Lin 2001).

One trial (86 people) compared HBOT to extracorporeal shockwave therapy (ESWT) in a head-to-head manner (Wang 2011). Inclusion criteria were people with chronic non-healing diabetic foot ulcers of greater than three months duration. HBOT was delivered at ATA 2.5 for 90 minutes, five days per week up to 20 treatments. The trial reported the proportion of ulcers healed at the end of treatment, laser-Doppler perfusion, and cell proliferation and apoptosis.

Venous ulcers

Hammarlund 1994 used a treatment session of 2.4 ATA for 90 minutes to a total of 30 sessions over six weeks, and employed an air-breathing sham treatment on the same schedule. The trial recruited 16 participants who were required to have persistent venous ulcers for more than one year with arterial blood pressures at the ankle and great toe within the normal range when compared with upper limb pressure. The ulcers were matched in pairs by size during the randomisation process, and mean wound areas were similar at the time of entry into the trial. Participants were excluded if they were currently smoking or had chronic illnesses such as diabetes or connective tissue disorders. The recruitment period for this trial is not known, but was over one year. The comparator treatment was not specified. Participants were followed up to 18 weeks from enrolment and data were obtained on wound area and the presence or absence of complete healing. The trial did not report undertaking a sample size calculation and may have been underpowered to detect any statistically significant effect of treatment.

Mixed ulcers group

Kaur 2012 included 30 consenting patients with nonhealing ulcers, despite conventional therapy of more than 4 weeks duration and different comorbidities (diabetes, hypertension, varicose vein, vascular insufficiency).The patients were randomized into either the control group (receiving only conventional treatment) or the HBOT group (receiving conventional treatment in addition to HBOT; HBOT was delivered at 2.5 ATA for 90 min, 6 days a week, a total of 30 sessions). The different comorbidities were equally distributed between the experimental and the control group (5 x Diabetes mellitus, 6 x hypertension, 2 x varicose vein, 2 x vascular insufficiency). The study report a sample size calculation for the primary outcome “wound size reduction”. Participants were followed until the end of the treatment (30 days).

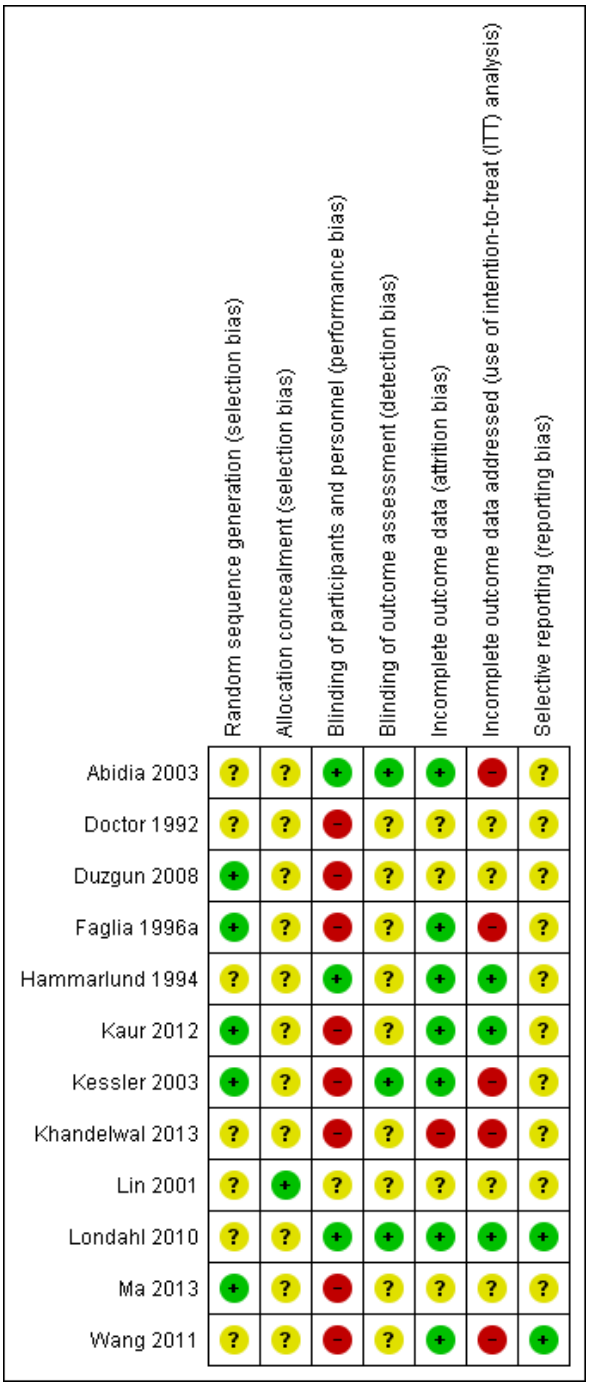
Excluded studies

We excluded 17 trials: six where allocation was not random (Holbach 1978; Baroni 1987; Oriani 1990; Zamboni 1997; Kalani 2000; Kalani 2002), two where the intervention of interest was topically applied oxygen (Heng 1984; Heng 2000), three where all participants received HBOT (Deng 2006; Efrati 2009; Kaya 2009), one dealing with acute burn wounds (Perrins 1967), one dealing with pelviperineal necrotising infections Cruz 2003, one which was an animal study (Whelan 2001) and one which was a study protocol with no further information available (Mathieu 2011). Three of the remaining reports were excluded as contributing no appropriate outcome data. (Faglia 1996b; Chin 2001) and an approach to contact the authors did not produce further data (see Characteristics of excluded studies).

Risk of bias in included studies

We estimated the risk of bias in each of these trials using the ’Risk of bias’ tables and the assessments have been graphically represented in Figure 1.

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



Allocation

Random sequence generation

Five trials (Faglia 1996a; Kessler 2003; Duzgun 2008; Kaur 2012; Ma 2013) described using random number tables to generate the randomisation sequence and we deemed them to be at low risk of bias for this domain. All of the other included trials did not report how the randomisation sequence was generated and we classified them as at unclear risk of bias.

Allocation concealment

Information that the allocation process was concealed was provided by the trial author for one trial (Lin 2001). We classified this trial as being at low risk of bias for this domain. Two trials reported using sealed envelopes but did not report that the envelopes were sequentially numbered and opaque (Abidia 2003; Londahl 2010). We classified these and all other included trials as at unclear risk of bias.

Blinding

Blinding of participants and personnel

Participants were blind to treatment group allocation in three trials (Hammarlund 1994; Abidia 2003; Londahl 2010) and we therefore classified them as low risk of bias. One trial reported that participants were not blinded and we classified it as high risk (Wang 2011). One trial does not specify the treatment of the control arm and we assessed this study as unclear risk of bias (Lin 2001). All other trials did not offer a sham treatment to the control arm and we therefore classified them as high risk of bias (Doctor 1992; Duzgun 2008; Faglia 1996a; Kaur 2012; Khandelwal 2013; Ma 2013).

Blinding of outcome assessment

Statements that outcome assessors were blind to participant group allocation were reported in three trials that we classified as low risk of bias for this domain (Abidia 2003; Kessler 2003; Londahl 2010). All other included trials did not provide any statement regarding blinding of the outcome assessment and we classified them as at unclear risk of bias.

Incomplete outcome data

Incomplete outcome data reported

The number of participants withdrawing/excluded from each treatment arm, along with reasons, was reported in thee trials (Faglia 1996a; Londahl 2010; Wang 2011). Londahl 2010 reported both an intention-to-treat (using all enrolled participants) and a 'per-protocol' analysis of those receiving at least 35 treatment sessions (11 participants allocated to HBOT and eight to sham). In the other trials there were no withdrawals or loss to follow-up that appeared in the analysis in any of the trials. One trial reported that all participants completed treatment (Hammarlund 1994). We classified these trials as low risk. One trial (Khandelwal 2013) reported numbers of lost participants during follow-up, however, without reporting reasons for withdrawal. Therefore, we classified this trial as high risk of bias.All of the other included trials did not provide a statement regarding attrition and we classified them as unclear risk. The numbers of participants lost to final follow-up are summarised in Table 1. Overall, there were 49 participants lost to final follow-up (8.5% of the total number enrolled).

Incomplete outcome data addressed

We classified one trial reporting that all recruited participants completed the intervention (Hammarlund 1994) as at low risk of bias. One trial reporting attrition of 22% in the HBOT arm presented both a per-protocol (> 35 treatment sessions) and an intention-to-treat analysis (Londahl 2010). We also classified this trial as being at low risk of bias. One trial reported an intention-to-treat design, but excluded participants who withdrew from the final analysis (Abidia 2003), and two trials indicated that some participants who were randomised were not included in the analysis (Faglia 1996a; Kessler 2003). One trial (Khandelwal 2013) reported numbers of lost participants during follow-up, however, it is unclear whether the analysis was performed on an intention-to-treat basis. We judged these trials as being at high risk of bias. Another trial presenting results for an analysis of completers, reported an imbalance of patient numbers withdrawing and the reasons for withdrawal between treatment arms, this trial was judged to be at high risk of bias (Wang 2011).

Selective reporting

We classified one trial for which a protocol was available as being at low risk of bias (Londahl 2010). For another trial, all outcomes detailed on a trials register were presented in the published report (Wang 2011). We also classified this trial as low risk of bias. For the remainder of the included published trials, no full protocol was

available for inspection. As such, we classified all other included trials as unclear risk of bias for this domain.

Effects of interventions

See: **Summary of findings for the main comparison** Hyperbaric Oxygen Therapy for chronic wounds

Diabetic foot ulcers (10 trials)

Primary outcomes

We did not pre specify in the protocol for this review that we anticipated multiple time points and we have presented data as reported in the included trials.

Proportion of ulcers healed at end of treatment period (six weeks)

Five trials reported this outcome (Abidia 2003; Kessler 2003; Londahl 2010; Ma 2013; Khandelwal 2013), involving 205 participants (39% of the total people with diabetes in this review), with 99 participants randomised to sham or control and 106 to hyperbaric oxygen therapy (HBOT). The trial by Khandelwal 2013 contributes 75.1% of the weight to this analysis. Ma 2013 reported in both arms of the study no events. Therefore, this study was excluded from this meta-analysis. There was a statistically significant increase in the proportion of ulcers healed following HBOT compared with control (P = 0.01) (risk ratio (RR) 2.35, 95% confidence interval (CI) 1.19 to 4.62 ; I^2 = 4%) (Analysis 1.1). The pre-planned sensitivity analysis examining the effect of allocation of drop-outs suggested a benefit with HBOT in the best-case scenario but not the worst-case scenario (best-case RR 4.61, 95% CI 2.35 to 9.08; P <0.00001, worst-case RR 0.84, 95% CI 0.51 to 1.37, P = 0.48) (Analysis 1.2; Analysis 1.3).

In terms of risk of bias, only two of the trials contributing to these analyses provided detail of the randomisation process (Kessler 2003; Ma 2013) and none reported allocation concealment. Only two studies performed blinding of patients (Abidia 2003; Londahl 2010) and were considered as low risk; Kessler 2003; Khandelwal 2013; and Ma 2013 were assessed as high risk of performance bias due to study design (no sham therapy). Three were considered to be at low risk of bias in terms of blinded outcome assessment (Abidia 2003; Kessler 2003; Londahl 2010) and two were considered to be at unclear risk (Khandelwal 2013; Ma 2013). Only Londahl 2010 presented a valid intention-to treat by including all participants randomised in the final analysis and was considered at low risk of attrition bias. Abidia 2003 , Kessler 2003, and Khandelwal 2013 each excluded participants who withdrew from their analyses and were at high risk of bias for this domain.

One trial with 41 participants (47 ulcers) assigned to extracorporeal shockwave therapy (ESWT) and 45 participants (47 ulcers) to HBOT (Wang 2011) reported this outcome. The unit of analysis reported was ulcers and the investigators reported a per-protocol analysis showing a statistically significant difference in the proportion of ulcers healed following HBOT compared with ESWT following treatment (P = 0.003). However, as the number of participants healing was not reported the findings could not be confirmed. This trial was considered to be at high risk of performance bias and at high risk of attrition bias as participants who withdrew were excluded from the analysis.

Proportion of ulcers healed at six months

Two trials (112 participants) involved 30% of the total diabetic population in this review (Abidia 2003; Londahl 2010), with 54 participants randomised to sham or control and 58 to HBOT. There was no significant increase in the proportion of ulcers healed following HBOT (RR 1.70, 95% CI 0.90 to 3.20, P = 0.10, I^2 = 0%) (Analysis 1.4). The sensitivity analysis examining the effect of allocation of drop-outs suggested a benefit with HBOT only in the best-case scenario (RR 2.71, 95% CI 1.53 to 4.83, P = 0.0007, I^2 = 0%; worst-case: RR 0.93, 95% CI 0.57 to 1.54, P = 0.79, I^2 = 24%) (Analysis 1.5; Analysis 1.6). Neither trial reported on the randomisation or allocation process, but both reported that all participants and outcome assessors were blind to treatment allocation. However, only the trial by Londahl 2010 presented a valid intention-to -treat.

Proportion of ulcers healed at one year

Three trials involved 212 participants (58% of the total diabetic participants in this review) (Abidia 2003; Duzgun 2008; Londahl 2010), with 104 randomised to sham or control and 108 to HBOT. Two trials reported no ulcers healed in the control arm (Abidia 2003; Duzgun 2008). A high level of between-trial heterogeneity was evident for this comparison (I^2 = 85%). In the original review the data was analysed as failure to heal rather than ulcers healed and demonstrated a significant effect in favour of HBOT. For this update, we presented the RR of healing in order to facilitate ease of interpretation for the reader of the healing outcomes. The interpretation of the RR was that a summary estimate in which HBOT increased the occurrence of healing would have a RR > 1.00. The pooled random-effects model showed no statistically significant difference between the groups (RR 9.53, 95% CI 0.44 to 207.76; P = 0.15) (Analysis 1.7). This change in the result is mainly due to the fact that there are a small number of trials with small sample sizes, two of which have no events in the control arm. We took statistical advice which indicated that this made the random-effects model for RR of healing unstable in these circumstances and repeated the analysis using a Peto odds ratio (OR) (OR, 7.58, 95% CI 4.33 to 13.29; P <0.00001) (Analysis 1.8). However, we must approach all these results with caution.

The sensitivity analysis examining the effect of allocation of drop-outs shows no statistically significant difference between the two

groups in either best-case or worst-case scenario (Analysis 1.9; Analysis 1.10). The trial by Duzgun 2008 was judged to be at overall unclear risk of bias.

Proportion of participants requiring major amputation

Five trials (309 participants) reported this outcome at final follow-up (Doctor 1992 (at discharge); Faglia 1996a (seven weeks); Abidia 2003; Londahl 2010 (one year) and Duzgun 2008 (up to 92 weeks)); 159 were randomised to HBOT, 150 to sham or control. There was no statistically significant reduction in amputation rate with the application of HBOT (the RR of major amputation with HBOT was 0.36, 95% CI 0.11 to 1.18, P = 0.08, I^2 = 50%) (Analysis 1.11). This result was sensitive to the assumptions made about drop-outs (best-case RR of amputation 0.20, 95% CI 0.10 to 0.38, P < 0.00001, worst-case 0.62, 95% CI 0.13 to 2.98, P = 0.55) (Analysis 1.12; Analysis 1.13). Subgroup analysis by number of treatments did not significantly affect this outcome, with a RR for amputation after 30 or more treatments of 0.40 (95% CI 0.07 to 2.23, P = 0.29). For < 30 treatments the RR was 0.29, 95% CI 0.07 to 1.16, P = 0.08 (Analysis 1.11). A *post hoc* subgroup analysis according to the use of sham therapy compared with no sham indicated a significant effect of treatment effect only amongst trials with no sham procedure as control (RR of amputation, HBOT compared with sham 0.47, 95% CI 0.09 to 2.44, P = 0.37; RR HBOT compared to control without sham 0.15, 95% CI 0.06 to 0.36, P < 0.0001) (Analysis 1.14). The trial by Doctor 1992 was judged to be at high risk of performance bias and all other methodological quality aspects as unclear risk of bias. The trial by Faglia 1996a was judged as unclear risk of selection bias, performance bias, detection bias and reporting bias, and as at high risk of performance bias and attrition bias as participants who withdrew were excluded from the analysis. The study by Duzgun 2008 were considered as high risk of performance bias as the control arm did not receive a sham treatment.

Secondary outcomes

Proportion of participants requiring minor amputation

Four trials (242 participants) reported this outcome at final follow-up (Doctor 1992; Abidia 2003; Duzgun 2008; Londahl 2010), 123 were randomised to HBOT compared with 119 to sham or control. There was no statistically significant change in rates of minor amputation with the application of HBOT (the RR of minor amputation with HBOT was 0.76, 95% CI 0.19 to 3.10, P = 0.71, I^2 = 70%) (Analysis 1.15). This result was not sensitive to the allocation of drop-outs (best-case RR of amputation 0.55, 95% CI 0.17 to 1.75, P = 0.31, I^2 = 63%, worst-case RR 0.91, 95% CI 0.21 to 4.02, P = 0.90, I^2 = 75%) (Analysis 1.16; Analysis 1.17). The analyses for this outcome may be subject to considerable between-trial heterogeneity as indicated by the high I^2 values (random effects), and these pooled results should be treated with caution.

Transcutaneous oxygen tension change in affected foot after treatment

Only one trial contributed results to this outcome (Faglia 1996a) involving 70 participants, 36 randomised to HBOT and 34 to a control regimen. Two participants were not included in the analysis (one control, one HBOT). There was a significantly greater increase in transcutaneous oxygen tension following HBOT (HBOT 14 mmHg, sham 5 mmHg, mean difference (MD) 9 mmHg, 95% CI 4.7 to 13.3, P = 0.0001) (Analysis 1.18). However this is a surrogate outcome measure and was not pre specified in the protocol for this review.

Absolute transcutaneous oxygen tensions in affected foot after treatment

Three trials (117 participants) (Faglia 1996a; Lin 2001; Abidia 2003) randomised 62 people to HBOT, 55 to control. Faglia 1996a contributed 59% of the participants to this analysis, and four participants were not included in the final analysis (two control, two HBOT). Transcutaneous oxygen tensions in the affected foot were significantly higher in those participants who had received HBOT (HBOT 11.8 mmHg higher, 95% CI 5.7 to 17.8, P = 0.0002, I^2 = 25.4%) (Analysis 1.19). However this is a surrogate outcome measure and was not pre specified in the protocol for this review.

Wound size reduction

Two trials (63 participants) reported this outcome (Kessler 2003; Ma 2013). The trial from Kessler 2003 (27 participants) suggested ulcer healing was more rapid initially following treatment (after two weeks ulcers in the HBOT group had reduced by 41.8%, compared with 21.7% in the control group). A significant difference was reported (P = 0.04). However, four weeks following the completion of therapy there was no difference in the mean ulcer area reduction between the two groups (HBOT 48.1% versus 41.7%, MD 6.4%, 95% CI -15.3 to 28.1) (Analysis 1.20). This is a small trial which did not report a sample size calculation and may have been underpowered to detect any statistically significant effect. Whilst no between-group differences in mean ulcer size or duration at baseline were evident from the trial report, no covariate adjusted analyses were reported as being undertaken. The trial recruited people with " early diabetic feet", Wagner grades 0, 1 or 2. The addition of the trial from Ma 2013 to the analysis suggested a statistically significant increased mean ulcer area reduction (P = 0.03) following HBOT compared with control at the end of the treatment (MD 18.10, 95% CI 1.40 to 34.79 ; I^2 = 54%) (Analysis 1.20).This trial contributes to 65.3% of the weight to this analysis.

Time to complete healing

No data were available for this outcome.

Quality of life

Only one trial reported a quality of life assessment in a subsequent publication to the original article (Londahl 2010). In this trial this outcome was assessed using the 36-Item Short-Form Health Survey (McHorney 1993) for 23 of 49 participants assigned to HBOT and 10 of 45 participants assigned to control at the one-year follow-up. A significant improvement in the physical function role limitations due to emotional health and mental health summary score was reported in the HBOT group (P < 0.05). No statistically significant improvements were reported for any domain amongst the control group. There was no difference between the two groups on the overall physical summary score (MD -0.20, 95% CI -8.58 to 8.18, P = 0.96), or the overall mental summary score (MD 6.60, 95% CI -3.93 to 17.13, P = 0.22) (Analysis 1.21; Analysis 1.22).

Recurrence rate

No data were available for this outcome.

Venous ulcers (1 trial)

Primary outcomes

Proportion of ulcers healed at 18 weeks

One trial (16 participants) (Hammarlund 1994) randomised nine people to HBOT and eight to sham. There was no statistically significant increase in the proportion of ulcers healed in the HBOT group compared with sham treatment (RR 5.00, 95% CI 0.28 to 90.18, P = 0.28) (Analysis 2.1). The sensitivity analysis examining the effect of allocation of drop-outs using a best-case (all drop-outs in active group deemed successes, all drop-outs in sham group deemed failures) and worse-case (all drop-outs in the active group deemed failures, all in the sham group deemed successes) did not alter the result (best-case RR 9.00, 95% CI 0.56 to 143.89, P = 0.12, worst-case RR 0.67, 95% CI 0.15 to 2.98, P = 0.60) (Analysis 2.2; Analysis 2.3).

In terms of risk of bias, the study did not report methods for the randomization process, for concealment of allocation or for blinding of outcome assessors and was considered to be at unclear risk of bias for these domains. However participants were blinded and there were no withdrawals from the study.

Secondary outcomes

Reduction in wound area immediately after treatment (six weeks)

Hammarlund 1994 found a significantly greater reduction in wound area following HBOT. No between-group differences in mean or median ulcer size were evident at baseline. Ulcer duration at baseline was not reported, although inclusion criteria was for ulcers >1 year. No covariate adjusted analyses were reported. This small trial did not report a sample size calculation and may have been underpowered to detect any statistically significant effect. There was a reduction in wound area in the HBOT group of 35.7% compared with 2.7% in the sham group (MD 33.00%, 95% CI 18.97 to 47.03, P < 0.00001) (Analysis 2.4).

Reduction in wound area at 18 weeks

Hammarlund 1994 reported that five participants were not included in this analysis (three sham, two HBOT). There was no significant difference in wound area reduction (HBOT 55.8%, sham 29.6%; MD 29.6%, 95% CI -23.0 to 82.2, P = 0.27) (Analysis 2.5).

Quality of life, pain reduction and recurrence rates for venous ulcers

No data were available for these outcomes.

Mixed ulcers (1 trial)

Primary outcomes

Healed at end of treatment (30 days)

Kaur 2012 enrolled patients with non-healing diabetic ulcers as well as venous ulcers ("mixed ulcers types") and reported this outcome. The trial involved 30 participants, treated for 30 days, with 15 participants randomised to control and 15 to HBOT.

There was no statistically significant increase in the proportion of ulcers healed following HBOT compared with control (P = 0.19) (RR 7.0, 95% CI 0.39 to 124.83) (Analysis 3.1).

In terms of risk of bias, the study provided details of the randomization process but did not report methods for concealment of allocation. The study was considered to be at unclear risk of bias in terms of blinding of outcome assessors and high risk of bias in terms of blinding of patients and personnel. No withdrawals were described.

Major amputations

Kaur 2012 reported this outcome at the end of treatment (30 days). There was no statistically significant reduction in the amputation rate with the application of HBOT (RR 0.2, 95% CI 0.03 to 1.51, P = 0.12) (Analysis 3.2).

Secondary outcomes

Periwound transcutaneous oxygen tensions at the end of treatment

Kaur 2012 reported after 30 days, periwound TcPO2 improved by 11.8 mgHg in the HBOT group (P = 0.01) and decreased by 5.7 mgHg from baseline value in the control group (P = 0.2). The baseline TcPO2 values were not statistically different between both groups (P = 0.407). The periwound transcutaneous oxygen tensions in the affected tissue were significantly higher in those participants who had received HBOT (HBOT 11.8 mmHg higher, 95% CI 5.7 to 17.8, P = 0.0002, I^2 = 25.4%) (Analysis 3.3).

Ulcer area reduction (%)

Kaur 2012 found a significantly greater reduction in wound area following HBOT. No between-group differences in the wound tissue score were evident at baseline. Ulcer duration at baseline was more than 4 weeks with median wound duration of 2 month (interquartile range (IQR) 1-60) in the HBOT group compared to 2.5 month (IQR 1-36) in the control group. There was a reduction in wound area in the HBOT group of 59.27% compared with -2.61% in the control group (MD 61.88%, 95% CI 41.91 to 81.85, P < 0.00001) (Analysis 3.4).

Arterial and pressure ulcers

No eligible trials were identified investigating the use of HBOT for these ulcers.

Adverse effects of HBOT

Two trials (Doctor 1992; Abidia 2003) stated explicitly that there were no complications or adverse events as a result of HBOT. Kessler 2003 reported one person in the HBOT group who was removed from the trial due to barotrauma of the ear and in Londahl 2010, two participants were removed from treatment because of claustrophobia - one in each arm of this sham-controlled trial. Kaur 2012 reported in the HBOT group three patients with ear pain, two patients with claustrophobia, one patient with tinnitus, and one patient with headache. The other trials did not report on adverse events or complications of therapy in either arm.

Summary of Findings Table

We have included a Summary of Findings table in this review (Summary of findings for the main comparison), which gives a concise overview and synthesis of the volume and quality of the evidence. The Summary of Findings table confirms our conclusion that the evidence is of moderate quality and on balance there is no strong evidence of a benefit of using HBOT for healing foot ulcers in people with diabetes.

DISCUSSION

This review has included data from twelve trials, ten of which recruited people with diabetic foot ulcers. We believe these represent all randomised controlled trials (RCTs) in this area, both published and unpublished at the time of searching the databases. For the update, we presented a risk ratio (RR) of healing with hyperbaric oxygen therapy (HBOT), as opposed to a RR of failing to heal without HBOT (i.e. control) as presented in the original review. This was undertaken in order to facilitate ease of interpretation of the healing outcomes for users of this review. We found evidence from five trials that the addition of HBOT to a standard wound care regimen results in a significant improvement in wound healing by six weeks (RR 2.35; P = 0.01), but this benefit is not evident at longer-term follow-up (RR at one year or longer 9.53; P = 0.15). This was in contrast to this outcome presented as the RR of failing to heal with control, as presented in the original review, which was significant. However, the RR of healing at 12 months presented here should be interpreted with caution given that the analyses included trials of varying sizes, some of which had no healing events in the control arm. As such, the pooled estimation may be unreliable. Although we found some indication amongst the included trials that HBOT may decrease the major amputation rate in people with diabetic foot lesions, our pooled estimate was not statistically significant (RR 0.36, 95% CI 0.11 to 1.18, P = 0.08).

We found no evidence that HBOT increases the healing of venous ulcers, arterial or pressure ulcers.

Eleven trials with 491 participants in total were eligible for data pooling according to the planned analyses, and a meta-analysis was not possible for many of the outcomes of interest for this review. Amongst the majority of the included trials, the reporting of a number of aspects of trial conduct to inform the risk of bias assessment was unclear. Only one of the trials reported sufficient detail to indicate in most of the quality aspects low risk of bias (Londahl 2010; Figure 1). Blinding of participants was only reported in three trials (Hammarlund 1994; Abidia 2003; Londahl 2010) and blinding of outcome assessors was only reported in three trials (Abidia 2003; Kessler 2003; Londahl 2010). Trials where blinding was not undertaken may have introduced a performance and detection bias to the results. It is not clear which of these factors is the

more important in determining the different effect on the risk of major amputation when comparing those who were blinded with those who were not (Analysis 1.14). There is also a possibility that some of the included trials may have been underpowered to detect a statistically significant effect of HBOT on healing or amputation rates. Other limitations that should be considered include the variability in the participant inclusion criteria across trials and the nature and timing of outcome assessments. In particular, there is a possibility of clinical heterogeneity due to differential wound size or severity across trials at participant enrolment. The trial by Londahl 2010, for example, excluded all participants at high risk of major amputation. Excluding this trial from the analysis (data not presented) resulted in a significant effect of HBOT on decreasing the risk of major amputation (P = 0.009).

The included trials were published over a 22-year period up to 2014. We had planned to perform subgroup analyses with respect to wound grade at trial enrolment, oxygen dose (treatment profile and number of treatments) and comparator therapy, however the paucity of eligible trials and poor reporting suggested the majority of these analyses would not be informative, and we only performed some subgroup analyses in diabetic ulcer trials. Overall patient inclusion criteria were not standard across trials and were poorly reported in some trials. The oxygen dose at each treatment was fairly consistent across trials, the lowest being 2.2 ATA for some participants in Faglia 1996a, while the highest was 3.0 ATA in Doctor 1992. The total number of treatments was similar in all trials except Doctor 1992, where only four treatments were administered over four weeks. While subgroup analysis by treatment number suggests the benefit of HBOT on major amputation rate was significant with either the short course or long course (> 30 treatment course: RR 0.40, P = 0.29; < 30 treatment course: RR 0.29, P = 0.08,), this result should be interpreted with caution given the contribution of the trial by Londahl 2010 previously discussed. While all trials included in the meta-analysis compared HBOT with some form of 'standard' wound care, these comparator therapies were generally poorly described and could not form the basis for a meaningful subgroup analysis with the exception of the analysis of the use of a HBOT sham or no sham as comparator.

Pooled data for clinical outcomes of interest could only be performed for diabetic foot lesions with respect to the proportion healed, and the risk of major and minor amputation. The analysis of the rate of major amputation was heterogenous (I^2 = 50%), suggesting a between-study variance that could not be explained by random variability. The risk of bias of the included trials was variable. The limited reporting of trial methodology in some reports (Doctor 1992; Duzgun 2008) resulted in an unclear risk of bias associated with the effect estimates these trials contributed to the pooled analyses. There were likely to be clinical differences in the individuals recruited to the included trials. The trial by Londahl 2010 excluded participants where major amputation was likely, while the other trials included a wider range of severity. Subgroup analysis by the number of treatment sessions delivered did not assist in the interpretation of this heterogeneity. Furthermore, it is not clear if the surgical decision to amputate was made while blinded to treatment allocation. This is an important potential source of bias and thus a threat to validity.

In general, the findings of this review are comparable to those of a previous review (Wang 2003). Wang considered all published comparative trials and case series including at least five participants, and concluded that, while the included trials suggested that HBOT might be of benefit in nonhealing diabetic ulcers, the overall trial quality was poor and there was insufficient evidence to recommend an appropriate time to initiate therapy. Further high-quality RCTs were recommended to examine short and long-term risks and benefits.

For venous ulceration we retrieved only one small trial (Hammarlund 1994) which indicated a significant reduction in wound area at six weeks following the administration of HBOT (33% mean difference (MD) in area ulcerated, 95% CI 19 to 47). This effect did not persist to 18 weeks and there was no significant increase in the proportion of ulcers healed at any time. While this trial suffered considerable data loss at 18 weeks, these results were not sensitive to the allocation of drop-outs. For arterial and decubitus ulceration we could locate no eligible trials and therefore have no data on which to evaluate the efficacy of HBOT for these ulcers.

In this update, we identified one trial (Kaur 2012) which enrolled patients with different comorbidities and therefore different types of ulcers. Due to the possibility that in future more studies of this types will be found, we decided to add this as a new comparison termed "mixed ulcers types" to the analysis. For this "mixed ulcers" there was a significant benefit of HBOT in terms of reduction in ulcer area at the end of treatment (30 days) but no statistically significant difference in the healing rate of ulcers at the end of treatment or the rate of major amputation.

All of these findings are subject to a potential publication bias. While we have made every effort to locate further unpublished data, it remains possible that this review is subject to a positive publication bias, with generally favourable trials more likely to achieve reporting.

With regard to long-term outcomes following HBOT, we have located no relevant data. Only one trial reported a quality of life assessment in a parallel publication (Londahl 2010), where no between-group differences in the physical or mental health summary scores of the SF-36 were evident. However, data were reported only for the completers of the quality of life assessment and as such an attrition bias may be present in the quality of life results. One trial evaluated the economic impact of the application of HBOT (Abidia 2003) and this trial suggested a saving of GBP 2960 on average per patient in the year following the HBOT. The savings were related to a large reduction in the number of visits required

for dressings in the first year (34 versus 137). However, reliability of this analysis is not clear. The methodology was not reported and we have no information regarding the influence of treatment allocation on clinical decisions made during the period of economic evaluation. Therefore, these findings should be handled with caution until more valid data are available.

None of the included trials reported major adverse outcomes in either arm, and therefore we can report no data relating to risk with which to balance the benefit estimated. HBOT is regarded as a relatively benign intervention. There are few major adverse effects (pulmonary barotrauma, drug reactions, injuries or death related to chamber fire) and while these are all rare enough not to expect to see them in the trials included in this review, they should be included in consideration of the benefit of this therapy. In practice it is likely that a beneficial effect strong enough to be clearly identified in clinical trials would overwhelm the consideration of such rare events. There are however, a number of more minor complications that may occur commonly and several authors reported on these. Visual disturbance, usually reduction in visual acuity secondary to conformational changes in the lens, is very commonly reported - perhaps as many as 50% of those having a course of 30 treatments (Khan 2003). While the great majority of participants recover spontaneously over a period of days to weeks, a small proportion of participants continue to require correction to restore sight to pre-treatment levels. The second most common adverse effect associated with HBOT is aural barotrauma. Barotrauma can affect any air-filled cavity in the body (including the middle ear, lungs and respiratory sinuses) and occurs as a direct result of compression. Aural barotrauma is by far the most common as the middle ear air space is small, largely surrounded by bone and the sensitive tympanic membrane, and usually requires active effort by the patient in order to inflate the middle ear through the Eustachian tube on each side. Barotrauma is thus not a consequence of HBOT directly, but rather of the physical conditions required to administer it. Most episodes of barotrauma are mild, easily treated or recover spontaneously and do not require the therapy to be abandoned.

AUTHORS' CONCLUSIONS

Implications for practice

There is some evidence that the addition of HBOT to a standard wound care regimen in people with foot ulcers due to diabetes results in a significant improvement in wound healing by six weeks, but this benefit is not evident at longer-term follow-up at one year or longer. In terms of amputation, HBOT does not appear to significantly improve the minor amputation rate in people with foot ulcers due to diabetes, while a potentially important effect on major amputation cannot be confirmed on this analysis. These findings are limited by trials recruiting small numbers of participants with diverse wound characteristics and by trial reporting and methodological discrepancies that present the potential to bias results. As such, these findings require a cautious interpretation. To date no informative conclusions regarding the effects of HBOT for chronic wounds with other underlying pathologies can be made.

Implications for research

There is a strong case for further better-reported, large randomised trials of high methodological rigour in order to define the true extent of benefit from the administration of HBOT. Specifically, more information is required on the subset of disease severity or classification most likely to benefit from this therapy, the time for which we can expect any benefits to persist, and the oxygen dose most appropriate. An economic evaluation should also be undertaken. Any future trials would need to consider in particular:

- appropriate sample sizes with power to detect expected differences;
- careful definition and selection of target participants;
- appropriate oxygen dose per treatment session (pressure and time);
- appropriate comparator therapy;
- use of an effective sham therapy;
- effective and explicit blinding of outcome assessors and surgeons;
- appropriate outcome measures including all those listed in this review;
- careful elucidation of any adverse effects; and
- the cost-utility of the therapy.

There is a strong case for investigation of the effects of HBOT on chronic wounds due to venous disease, arterial disease and pressure damage, in large, rigorous randomised clinical trials. Future trials should consider the items and outcomes as stated above for diabetic foot ulcers.

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REFERENCES

References to studies included in this review

Abidia 2003 *{published data only}*

Abidia A, Kuhan G, Laden G, Bahia H, Johnson B, Wilkinson A, et al. Hyperbaric oxygen therapy for diabetic leg ulcers - a double-blind randomised-controlled trial. *Undersea and Hyperbaric Medicine* 2001;**28**(Suppl):64.

Abidia A, Kuhan G, Laden G, Bahia H, Johnson B, Wilkinson A, et al. Role of hyperbaric oxygen therapy in ischaemic, diabetic, lower-extremity ulcers: a double-blind randomized controlled study. *British Journal of Surgery* 2001;**88**(5):744.

Abidia A, Kuhan G, Laden G, et al. The role of hyperbaric oxygen therapy in ischaemic, diabetic, lower-extremity ulcers: a double-blind randomized controlled study. *Undersea and Hyperbaric Medicine* 2001;**28**:48.

* Abidia A, Laden G, Kuhan G, Johnson BF, Wilkinson AR, Renwick PM, et al. The role of hyperbaric oxygen therapy in ischaemic diabetic lower extremity ulcers: a double-blind randomised-controlled trial. *European Journal of Vascular and Endovascular Surgery* 2003;**25**:513–8.

Doctor 1992 *{published data only}*

Doctor N, Pandya S, Supe A. Hyperbaric oxygen therapy in diabetic foot. *Journal of Postgraduate Medicine* 1992;**38**(3): 112–4.

Duzgun 2008 *{published data only}*

Duzgun AP, Satir HZ, Ozozan O, Saylam B, Kulah B, Coskun F. Effect of hyperbaric oxygen therapy on healing of diabetic foot ulcers. *Journal of Foot and Ankle Surgery* 2008; **47**(6):515–9.

Faglia 1996a *{published data only}*

Faglia E, Favales F, Aldeghi A, Calia P, Quarantiello A, Oriani G, et al. Adjunctive systemic hyperbaric oxygen therapy in treatment of severe prevalently ischemic diabetic foot ulcer. A randomized study. *Diabetes Care* 1996;**19**(12): 1338–43.

Hammarlund 1994 *{published data only}*

Hammarlund C, Sundberg T. Hyperbaric oxygen reduced size of chronic leg ulcers: a randomized double-blind study. *Plastic and Reconstructive Surgery* 1994;**93**(4):829–33.

Kaur 2012 *{published data only}*

Kaur S, Pawar M, Banerjee N, Garg R. Evaluation of the efficacy of hyperbaric oxygen therapy in the management of chronic nonhealing ulcer and role of periwound transcutaneous oximetry as a predictor of wound healing response: A randomized prospective controlled trial. *J Anaesthesiol Clin Pharmacol* 2012;**28**:70–5.

Kessler 2003 *{published data only}*

Kessler L, Bilbault P, Ortéga F, Grasso C, Passemard R, Stephan D, et al. Hyperbaric oxygen accelerates the healing rate of nonischemic chronic diabetic foot ulcers. *Diabetes Care* 2003;**26**:2378–82.

Khandelwal 2013 *{published data only}*

Khandelwal S, Chaudhary P, Poddar D D, Saxena N, Singh R A, Biswal U C. Comparative Study of Different Treatment Options of Grade III and IV Diabetic Foot Ulcers to Reduce the Incidence of Amputations. *Clin Pract* 2013;**3**:e9.

Lin 2001 *{published and unpublished data}*

Lin TF, Chen SB, Niu KC. The vascular effects of hyperbaric oxygen therapy in treatment of early diabetic foot. *Undersea and Hyperbaric Medicine* 2001;**28**(Suppl):67.

Londahl 2010 *{published data only}*

Löndahl M, Landin-Olsson M, Katzman P. Hyperbaric oxygen therapy improves health-related quality of life in patients with diabetes and chronic foot ulcer. *Diabetic Medicine* 2011;**28**(2):186–90.

* Löndahl M, Nilsson A, Katzman P, Hammarlund C. Hyperbaric oxygen therapy as adjunctive treatment of chronic diabetic foot ulcers. *Diabetes Care* 2010;**33**(5): 998–1003.

Ma 2013 *{published data only}*

Ma L, Li P, Shi Z, Hou T, Chen X, Du J. A prospective, randomized, controlled study of hyperbaric oxygen therapy: effects on healing and oxidative stress of ulcer tissue in patients with a diabetic foot ulcer. *Ostomy Wound Manage* 2013;**59**:18–24.

Wang 2011 *{published data only}*

Wang C-J, Wu R-W, Yang Y-J. Treatment of diabetic foot ulcers: a comparative study of extracorporeal shockwave therapy and hyperbaric oxygen therapy. *Diabetes Research and Clinical Practice* 2011;**92**(2):187–93.

References to studies excluded from this review

Baroni 1987 *{published data only}*

Baroni G, Porro T, Faglia E, Pizzi G, Mastropasqua A, Oriani G, et al. Hyperbaric oxygen in diabetic gangrene treatment. *Diabetes Care* 1987;**10**:81–6.

Chin 2001 *{published data only}*

Chin K, Xie Y, Abidia A, Laden G, Greenman J, Monson J, et al. The relationship of hyperbaric oxygen therapy

and vascular endothelial growth factor in diabetic patients with leg ulcers: a double-blind randomised controlled trial. *Undersea and Hyperbaric Medicine* 2001;**28**(Suppl):63.

Cruz 2003 *{published data only}*
Cruz NR. Evaluation of the effect of hyperbaric oxygen therapy in the treatment of pelviperineal necrotizing

infections [Avaliaçã o do efeito da oxigenoterapia

hiperbárica no tratamento das infecçõ es necrosantes pelviperineais]. PhD Thesis. Universidade de São Paulo. Faculdade de Medicina. Departamento de Cirurgia 2003.

Deng 2006 *{published data only}*
Deng LL, Lin JX. Nursing of diabetic foot treated by oxygen therapy and external application of Long Xue Jie. *Academic Journal of Guangzhou Medical College* 2006;**34**(3):65–6.

Efrati 2009 *{published data only}*
Efrati S, Gall N, Bergan J, Fishlev G, Bass A, Berman S, et al. Hyperbaric oxygen, oxidative stress, NO bioavailability and ulcer oxygenation in diabetic patients. *Undersea and Hyperbaric Medicine* 2009;**36**(1):1–12.

Faglia 1996b *{published data only}*
Faglia E, Favales F, Aldeghi A, Calia P, Quarantiello A, Oriani G, et al. Adjunctive systemic hyperbaric oxygen therapy in treatment of diabetic foot ulcer. A randomised study. Proceedings of the International Joint Meeting on Hyperbaric and Underwater Medicine. Bologna: Grafica Victoria, 1996:391–9.

Heng 1984 *{published data only}*
Heng MC, Pilgrim JP, Beck FW. A simplified hyperbaric oxygen technique for leg ulcers. *Archives of Dermatology* 1984;**120**(5):640–5.

Heng 2000 *{published data only}*
Heng MC, Harker J, Csathy G, Marshall C, Brazier J, Sumampong S, et al. Angiogenesis in necrotic ulcers treated with hyperbaric oxygen. *Ostomy Wound Management* 2000; **46**(9):18-28, 30-2.

Holbach 1978 *{published data only}*
Holbach KH. Indications for and results of hyperbaric oxygenation. *Hefte für Unfallheilkunde* 1978;**132**:214–7.

Kalani 2000 *{published data only}*
Kalani M, Naderi N, Lind F. Hyperbaric oxygen therapy for wound healing and limb salvage in diabetic foot lesions: three year follow-up. *Undersea and Hyperbaric Medicine* 2000;**27**(Suppl):44–5.

Kalani 2002 *{published data only}*
Kalani M, Jorneskog G, Naderi N, Lind F, Brismar K. Hyperbaric oxygen (HBO) therapy in treatment of diabetic foot ulcers. Long-term follow-up. *Journal of Diabetes and its Complications* 2002;**16**(2):153–8.

Kaya 2009 *{published data only}*
Kaya A, Aydin F, Altay T, Karapinar L, Ozturk H, Karakuzu C. Can major amputation rates be decreased in diabetic foot ulcers with hyperbaric oxygen therapy?. *Int Orthop* 2009; **33**:441–6.

Londahl 2011 *{published data only}*
* Londahl M, Katzman P, Hammarlund C, Nilsson A, Landin-Olsson M. Relationship between ulcer healing after hyperbaric oxygentherapy and transcutaneous oximetry, toe blood pressureand ankle-brachial index in patients with diabetesand chronic foot ulcers. *Diabetologia* 2011;**54**:65-8.
Londahl M, Katzman P, Nilsson A, Hammarlund C, Landin-Olsson M. Transcutaneous oximetry is a useful predictor of foot ulcer healing rate and patient selection to hyperbaric oxygen treatment (HBOT). Diabetes Conference: 70th Scientific Sessions of the American Diabetes Association Orlando, FL United States. 2010.

Mathieu 2011 *{unpublished data only}*
Mathieu D, et al. HBO in the treatment of diabetic foot lesions (Study protocol). http://www.oxynet.org/ProtocolsIndex.htm (accessed 27 October 2011).

Oriani 1990 *{published data only}*
Oriani G, Meazza D, Favales F, Pizzi GL, Aldeghi A, Faglia E. Hyperbaric oxygen therapy in diabetic gangrene. *Journal of Hyperbaric Medicine* 1990;**5**(3):171–5.

Perrins 1967 *{published data only}*
Perrins DJ. Influence of hyperbaric oxygen on the survival of split skin grafts. *Lancet* 1967;**1**(7495):868–71.

Whelan 2001 *{published data only}*
Whelan HT, Buchmann EV, Dhokalia A, Kane MP, Whelan NT, Wong-Riley MT, et al. Effect of NASA light-emitting diode irradiation on molecular changes for wound healing in diabetic mice. *Journal of Clinical Laser Medicine and Surgery* 2001;**21**(2):67–74.

Zamboni 1997 *{published data only}*
Zamboni WA, Wong HP, Stephenson LL, Pfeifer MA. Evaluation of hyperbaric oxygen for diabetic wounds: a prospective study. *Undersea and Hyperbaric Medicine* 1997; **24**(3):175–9.

References to ongoing studies

O'Reilly 2011 *{published data only}*
O'Reilly D, Linden R, Fedorko L, Tarride JE, Jones WG, Bowen JM, et al. A prospective, double-blind, randomized, controlled clinical trial comparing standard wound care with adjunctive hyperbaric oxygen therapy (HBOT) to standard wound care only for the treatment of chronic, non-healing ulcers of the lower limb in patients with diabetes mellitus: a study protocol. *Trials* 2001;**12**:69.

Stoekenbroek 2015 *{published data only}*
Stoekenbroek RM, Santema TB, Koelemay MJW, van Hulst RA, Legemate DA, Reekers JA, Ubbink DT. Is additional hyperbaric oxygen therapy cost-effective for treating ischemic diabetic ulcers? Study protocol for the Dutch DAMOCLES multicenter randomized clinical trial. *Journal of Diabetes* 2015;**71**:125–32.

Additional references

Akbari Sari 2009
Akbari Sari A, Flemming K, Cullum NA, Wollina U. Therapeutic ultrasound for pressure ulcers. *Cochrane*

Database of Systematic Reviews 2006, Issue 3. [DOI: 10.1002/14651858.CD001275.pub2]

Allman 1997
Allman RM. Pressure ulcer prevalence, incidence, risk factors, and impact. *Clinical Geriatric Medicine* 1997;**13**: 421–36.

Amsler 2009
Amsler F, Willenberg T, Blattler W. In search of optimal compression therapy for venous leg ulcers: a meta-analysis of studies comparing divers bandages with specifically designed stockings. *Journal of Vascular Surgery* 2009;**50**: 668–74.

Andersson 1993
Andersson E, Hansson C, Swanbeck G. Leg and foot ulcer prevalence and investigation of the peripheral arterial and venous circulation in a randomised elderly population - an epidemiological survey and clinical investigation. *Acta Dermato-Venerologica* 1993;**73**:57–61.

Apelqvist 1993
Apelqvist J, Larsson J, Agardh CD. Long-term prognosis for diabetic patients with foot ulcers. *Journal Internal Medicine* 1993;**233**:485–91.

Aziz 2011
Aziz Z, Cullum NA, Flemming K. Electromagnetic therapy for treating venous leg ulcers. *Cochrane Database of Systematic Reviews* 2001, Issue 3. [DOI: 10.1002/14651858.CD002933.pub4]

Banwell 1999
Banwell PE. Topical negative pressure therapy in wound care. *Journal of Wound Care* 1999;**8**:79–84.

Bayati 1998
Bayati S, Russell RC, Roth AC. Stimulation of angiogenesis to improve the viability of prefabricated flaps. *Plastic and Reconstructive Surgery* 1998;**101**(5):1290–5.

Bosanquet 1992
Bosanquet N. Cost of venous ulcers from maintenance therapy to investment programmes. *Phlebology* 1992;**1**: 44–6.

Boulton 2008
Boulton JM. The diabetic foot - an update. *Foot and Ankle Surgery* 2008;**14**:120–4.

Callam 1985
Callam MJ, Ruckley CV, Harper DR, Dale JJ. Chronic ulceration of the leg: extent of the problem and provision of care. *British Medical Journal* 1985;**290**:1855–6.

Calman 1998
Calman K. On the state of the public health. *The Annual Report of the Chief Medical Officer of the Department of Health for the Year 1997*. London: The Stationery Office, 1998.

Chuck 2008
Chuck AW, Hailey D, Jacobs P, Perry DC. Cost-effectiveness and budget impact of adjunctive hyperbaric oxygen therapy for diabetic foot ulcers. *International Journal of Technology Assessment in Health Care* 2008;**24**(2):178–83.

Cianci 1993
Cianci P, Hunt TK. Adjunctive hyperbaric oxygen therapy in the treatment of diabetic wounds of the foot. In: Levin ME, O´ Neal LW, Bowker JH editor(s). *The Diabetic Foot*. 5th Edition. St. Louis: Mosby Year Book, 1993.

Clarke 2003
Clark JM, Thom SR. Oxygen under pressure. In: Brubakk AO, Neuman TS editor(s). *Bennett and Elliott's physiology and medicine of diving*. 5th Edition. London: Saunders, 2003:358–418.

Cullum 2010
Cullum NA, Al-Kurdi D, Bell-Syer SEM. Therapeutic ultrasound for venous leg ulcers. *Cochrane Database of Systematic Reviews* 2010, Issue 6. [DOI: 10.1002/14651858.CD001180.pub3]

Dealey 1994
Dealey C. *The Care of Wounds*. Oxford: Blackwell Scientific Publications, 1994.

Dimitrijevich 1999
Dimitrijevich SD, Paranjape S, Wilson JR, Gracy RW, Mills JG. Effect of hyperbaric oxygen on human skin cells in culture and in human dermal and skin equivalents. *Wound Repair and Regeneration* 1999;**7**(1):53–64.

Dumville 2011a
Dumville JC, Deshpande S, O'Meara S, Speak K. Foam dressings for healing diabetic foot ulcers. *Cochrane Database of Systematic Reviews* 2011, Issue 9. [DOI: 10.1002/14651858.CD009111.pub2]

Dumville 2011b
Dumville JC, O'Meara S, Deshpande S, Speak K. Hydrogel dressings for healing diabetic foot ulcers. *Cochrane Database of Systematic Reviews* 2011, Issue 9. [DOI: 10.1002/14651858.CD009101.pub2]

Edwards 2010
Edwards J, Stapley S. Debridement of diabetic foot ulcers. *Cochrane Database of Systematic Reviews* 2010, Issue 1. [DOI: 10.1002/14651858.CD003556.pub2]

Escaleira 2010
Escaleira R, Cardoso M, Rego J, Macedo P, Midões A. Efficacy of a two-component compression system for the therapy of venous leg ulcers. *Journal of Wound Care* 2010; **19**(3):104–9.

Fowkes 2008
Fowkes F, Leng GC. Bypass surgery for chronic lower limb ischaemia. *Cochrane Database of Systematic Reviews* 2008, Issue 2. [DOI: 10.1002/14651858.CD002000.pub2]

Higgins 2011
Higgins JPT, Altman DG (editors), on behalf of the Cochrane Statistical Methods Group and the Cochrane Bias Methods Group. Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Hohn 1976
Hohn DC, MacKay RD, Halliday B, Hunt TK. Effect of O2 tension on microbicidal function of leucocytes in wounds and in vitro. *Surgical Forum* 1976;**27**:18–20.

Humphrey 1996
Humphrey AR, Dowse GK, Thoma K, Zimmet PZ. Diabetes and nontraumatic lower extremity amputations. Incidence, risk factors, and prevention - a 12-year follow-up study in Nauru. *Diabetes Care* 1996;**19**:710–4.

Hunt 1972
Hunt TK, Pai MP. The effect of varying oxygen tensions on wound metabolism and collagen synthesis. *Surgical Gynaecology and Obstetrics* 1972;**135**:561–7.

Jain 1999
Jain KK. In: Jain KK editor(s). *Textbook of Hyperbaric Medicine*. 3rd Edition. Seattle: Hogrefe and Huber, 1999.

Jensen 1986
Jensen JA, Hunt TK, Scheuenstuhl H, Banda MJ. Effect of lactate, pyruvate and pH on secretion of angiogenesis and mitogenesis factors by macrophages. *Laboratory Investigations* 1986;**54**:574–8.

Jones 2009
Jones JE, Nelson EA. Skin grafting for venous leg ulcers. *Cochrane Database of Systematic Reviews* 2007, Issue 2. [DOI: 10.1002/14651858.CD001737.pub3]

Jull 2007
Jull AB, Arroll B, Parag V, Waters J. Pentoxifylline for treating venous leg ulcers. *Cochrane Database of Systematic Reviews* 2007, Issue 3. [DOI: 10.1002/14651858.CD001733.pub2]

Jull 2008
Jull AB, Rodgers A, Walker N. Honey as a topical treatment for wounds. *Cochrane Database of Systematic Reviews* 2008, Issue 4. [DOI: 10.1002/14651858.CD005083.pub2]

Khan 2003
Khan B, Evans AW, Easterbrook M. Refractive changes in patients undergoing hyperbaric oxygen therapy: a prospective study. *Undersea and Hyperbaric Medicine* 2003;**24**(Suppl):9.

Kindwall 1999
Kindwall EP, Whelan HT. In: Kindwall EP, Whelan HT editor(s). *Hyperbaric Medicine Practice*. 2nd Edition. Flagstaff: Best Publishing Company, 1999.

Knighton 1983
Knighton DR, Hunt TK, Schueuencstuhl H, Halliday BJ, Werb Z, Banda MJ. Oxygen tension regulates the expression of angiogenesis factor by macrophages. *Science* 1983;**221**:1283.

Kulonen 1968
Kulonen E, Niinikoski J. Effect of hyperbaric oxygenation on wound healing and experimental granuloma. *Acta Physiologica Scandinavia* 1968;**73**(3):383–4.

Langer 2003
Langer G, Knerr A, Kuss O, Behrens J, Schlömer GJ. Nutritional interventions for preventing and treating pressure ulcers. *Cochrane Database of Systematic Reviews* 2003, Issue 4. [DOI: 10.1002/14651858.CD003216]

Lauterbach 2010
Lauterbach S, Kostev K, Kohlmann T. Prevalence of diabetic foot syndrome and its risk factors in the UK. *Journal of Wound Care* 2010;**19**(8):333–7.

Lee 1993
Lee JS, Lu M, Lee VS, Russell D, Bahr C, Lee ET. Lower-extremity amputation. Incidence, risk factors, and mortality in the Oklahoma Indian Diabetes Study. *Diabetes* 1993;**42**:876–82.

Lees 1992
Lees TA, Lambert D. Prevalence of lower limb ulceration in an urban health district. *British Journal of Surgery* 1992;**79**:1032–4.

Lefebvre 2011
Lefebvre C, Manheimer E, Glanville J, on behalf of the Cochrane Information Retrieval Methods Group. Chapter 6: Searching for studies. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Marx 1990
Marx RE, Ehler WJ, Tayapongsak P, Pierce LW. Relationship of oxygen dose to angiogenesis induction in irradiated tissue. *American Journal of Surgery* 1990;**160**(5):519–24.

McHorney 1993
McHorney CA, Ware JE Jr, Raczek AE. The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. *Medical Care* 1993;**31**:247–63.

Niinikoski 1972a
Niinikoski J, Gunta-Grislis BA, Hunt TK. Respiratory gas tensions and collagen in infected wounds. *Annals of Surgery* 1972;**175**:588–93.

Niinikoski 1972b
Niinikoski J, Hunt TK. Measurement of wound oxygen with implanted silastic tube. *Surgery* 1972;**71**:22.

O'Dea 1999
O'Dea K. The prevalence of pressure damage in acute care hospital patients in the UK. *Journal of Wound Care* 1999;**8**:192–4. [MEDLINE: ODEA1999]

O'Meara 2009
O'Meara S, Cullum NA, Nelson EA. Compression for venous leg ulcers. *Cochrane Database of Systematic Reviews* 2009, Issue 1. [DOI: 10.1002/14651858.CD000265.pub2]

Oriani 1996
Oriani G, Marroni A, Wattel F. In: Oriani G, Marroni A, Wattel F editor(s). *Handbook on Hyperbaric Medicine*. 1st Edition. Milan: Springer, 1996. [MEDLINE: 3-540-75016-9]

Palfreyman 2006
Palfreyman SJ, Nelson EA, Lochiel R, Michaels JA. Dressings for healing venous leg ulcers. *Cochrane Database*

of Systematic Reviews 2006, Issue 3. [DOI: 10.1002/14651858.CD001103.pub2]

Rabkin 1988
Rabkin JM, Hunt TK. Infection and oxygen. In: Davis JC, Hunt TK editor(s). *Problem Wounds. The Role of Oxygen*. New York: Elsevier Science, 1988.

Reddy 2008
Reddy M, Gill SS, Kalkar SR, Wu W, Anderson PJ, Rochon PA. Treatment of pressure ulcers. A systematic review. *JAMA* 2008;**300**(22):2647–62.

RevMan 2014
The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). 5.3 beta. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Sheffield 1985
Sheffield PJ. Tissue oxygen measurements with respect to soft tissue wound healing with normobaric and hyperbaric oxygen. *Hyperbaric Oxygen Review* 1985;**6**:18–46.

Siddiqui 1997
Siddiqui A, Davidson JD, Mustoe TA. Ischemic tissue oxygen capacitance after hyperbaric oxygen therapy: a new physiologic concept. *Plastic and Reconstructive Surgery* 1997;**99**:148–55.

SIGN 1997
Scottish Intercollegiate Guidelines Network. Management of diabetic foot disease. Implementation of the St. Vincent Declaration. The Care of Diabetic Patients in Scotland 1997.

SIGN 2011
Scottish Intercollegiate Guidelines Network (SIGN). Search filters. Available from http://www.sign.ac.uk/methodology/filters.html#random (accessed 17 July 2011).

Singh 2005
Singh N, Armstrong DG, Lipsky BA. Preventing foot ulcers in patients with diabetes. *JAMA* 2005;**293**:217–28.

Stevens 1993
Stevens DL, Bryant AE, Adams K, Mader JT. Evaluation of therapy with hyperbaric oxygen for experimental infection with Clostridium perfringens. *Clinical Infectious Diseases* 1993;**17**(2):231–7.

Ubbink 2008
Ubbink DT, Westerbos SJ, Evans D, Land L, Vermeulen H. Topical negative pressure for treating chronic wounds. *Cochrane Database of Systematic Reviews* 2008, Issue 3. [DOI: 10.1002/14651858.CD001898.pub2]

UHMS 2001
The Hyperbaric Oxygen Therapy Committee of the Undersea and Hyperbaric Medical Society. *The Hyperbaric Oxygen Therapy Committee Report*. Kensington Ma: The Undersea and Hyperbaric Medical Society, 2001.

UHMS 2001a
Undersea and Hyperbaric Medical Society. Hyperbaric chambers North and Central America. A directory of hyperbaric treatment chambers. Undersea and Hyperbaric Medical Society Publications. Kensington, MD 2001.

Wagner 1987
Wagner FW. The diabetic foot. *Orthopedics* 1987;**10**(1):163–72.

Wang 2003
Wang C, Schwaitzberg S, Berliner E, Zarin D, Lau J. Hyperbaric oxygen for treating wounds: a systematic review of the literature. *Archives of Surgery* 2003;**138**:272–9.

Wysocki 1996
Wysocki AB. Wound fluids and the pathogenesis of chronic wounds. *Journal of Wound, Ostomy, and Continence Nursing* 1996;**23**:283–90.

Zhao 1994
Zhao LL, Davidson JD, Wee SC, Roth SI, Mustoe TA. Effect of hyperbaric oxygen and growth factors on rabbit ear ischemic ulcers. *Archives of Surgery* 1994;**129**(10):1043–9.

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Abidia 2003

Methods	Randomised controlled trial. Allocation concealed at enrolment. Participants, "carers" (including the surgeons) and observers ("medical assessors") blinded
Participants	18 people with diabetes with lower-extremity ulcers 1 to 10 cm in diameter that had not shown signs of healing > 6 weeks since presenting Group 1: 9 randomised Group 2: 9 randomised
Interventions	Group 1: hyperbaric air (control) Group 2: 100% oxygen (treatment) In a multi-place chamber via hood at a pressure of 2.4 atmospheres absolute (ATA) for 90 minutes daily, 5 days per week, totaling 30 sessions. All participants regularly attended a specialised multi-disciplinary clinic. Wound care was standardised for all participants. Antibiotic therapy was given if there were clinical signs of infection
Outcomes	Proportion of ulcers healed at week 6; at 6 months; at 1 year Reduction in ulcer size at 6 weeks; at 6 months Major amputation; major amputation Transcutaneous oxygen
Notes	Quality of life undertaken using SF-36 and HADS. Cost-effectiveness analysis also undertaken

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Mentions a "randomisation code" but no statement of how randomisation sequence was generated
Allocation concealment (selection bias)	Unclear risk	Quote: "The randomisation was performed using sealed envelopes and the randomisation code was only known to the chamber operator." Comment: no statement that the envelopes were sequentially numbered and opaque
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "All patients, their carers and medical assessors were blinded to the treatment. "

Abidia 2003 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All patients, their carers and medical assessors were blinded to the treatment. "
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Two patients withdrew during the course of the study (one in the control group required urgent vascular intervention and one in the treatment group dropped out for personal reasons)"
Incomplete outcome data addressed (use of intention-to-treat (ITT) analysis)	High risk	Quote: "Data analysis was on an intention-to-treat basis." "Two patients withdrew during the course of the study (one in the control group required urgent vascular intervention and one in the treatment group dropped out for personal reasons)" "At 6 weeks follow-up, complete healing was achieved in five out of eight ulcers in the treatment group compared with one out of eight ulcers in the control group." Comment: although an intention-to treat-design was stipulated, the two patients withdrawing were not included in the final analysis
Selective reporting (reporting bias)	Unclear risk	No protocol available. Most of the outcomes described in methods section are reported, however only the depression scale for HADS is reported and only as P values (significant)

Doctor 1992

Methods	Randomised controlled trial. No blinding reported
Participants	30 people with diabetes referred with chronic foot lesion Group 1: 15 Group 2: 15
Interventions	Group 1: HBOT at 3.0 ATA on 4 occasions over 4 weeks Group 2: standard care consisting of a specified surgical and dressing regimen
Outcomes	Major amputations Minor amputations Hospital stay Skin graft/stump healing/infection

Doctor 1992 (*Continued*)

	Positive wound cultures	
Notes	Unusual HBOT regimen	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "The patients were randomly allotted to one of the two groups" Comment: no description of sequence generation
Allocation concealment (selection bias)	Unclear risk	No statement on allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	No statement on blinding of patients. Since the control group received only conventional treatment and no sham therapy, the patients were unblinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No statement on blinding of outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No statement on withdrawals
Incomplete outcome data addressed (use of intention-to-treat (ITT) analysis)	Unclear risk	There is no statement as to whether the presented results are for all patients who entered the trial or otherwise
Selective reporting (reporting bias)	Unclear risk	No protocol available, but all outcomes in methods section are reported in results

Duzgun 2008

Methods	Randomised controlled trial of standard wound therapy versus standard therapy plus HBOT. No blinding attempted, but random number table used and primary outcome unlikely to be subject to bias
Participants	100 adults with diabetes requiring admission to hospital with "infected foot ulceration" for at least 4 weeks and who had received "appropriate local and systemic wound care" Group 1: 50 randomised Group 2: 50 randomised
Interventions	Group 1: standard care Group 2: HBOT Standard care "entailed daily wound care, including dressing changes and local debride-

	ment at bedside or in the operating room, as well as amputation when indicated. Infection controls were carried out by clinical follow-up, and by performing culture-antibiograms of surgically obtained specimens to determine appropriate antibiotic therapy." In the HBOT group, standard therapy was supplemented by 100% oxygen at 2.0 ATA for 90 minutes twice one day and once the next day, alternating for 20 to 30 days. Actual course probably determined by clinical response
Outcomes	Total closure of the wound without the need for surgical intervention (healed) Graft or flap closure required to attain healing Amputation distal to the metatarsophalangeal joints (distal amputation) Amputation proximal to the metatarsophalangeal joints (proximal amputation) No change Operative surgical debridement (in the operating room) of the wound was all that was required to achieve closure
Notes	Long course of HBOT

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "patients were randomly assigned.. .using a random number table"
Allocation concealment (selection bias)	Unclear risk	No statement on allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	No statement on blinding of patients. Since the control group received only standard treatment and no sham therapy, the patients were unblinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No statement on blinding of outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No statement on withdrawals
Incomplete outcome data addressed (use of intention-to-treat (ITT) analysis)	Unclear risk	There is no statement as to whether the presented results are an ITT analysis or that all participants completed the trial
Selective reporting (reporting bias)	Unclear risk	No protocol available, but all outcomes in methods section are reported in results

Faglia 1996a

Methods	Randomised controlled trial. No blinding reported
Participants	70 people with diabetes and a foot lesion Wagner grade 2 to 4 Group 1: 33 randomised Group 2: 37 randomised
Interventions	Group 1: standard care consisting of a specialised multidisciplinary wound management programme Group 2: HBOT at 2.2 to 2.5 ATA for 90 minutes on an average of 39 occasions over about 6 weeks
Outcomes	Major amputation Transcutaneous oxygen Minor amputations Vascular procedures
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Patients were allocated to treatment arms by consulting a table of random numbers at the hospital
Allocation concealment (selection bias)	Unclear risk	No statement on allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	No statement on blinding of patients. Since the control group received only conventional treatment and no sham therapy, the patients were unblinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No statement on blinding of outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	One HBOT patient refused treatment and one HBOT patient died
Incomplete outcome data addressed (use of intention-to-treat (ITT) analysis)	High risk	Quote: "Both these subjects were excluded from the analysis of the results."
Selective reporting (reporting bias)	Unclear risk	No protocol available, but all outcomes in methods section are reported in results

Hammarlund 1994

Methods	Randomised, double-blind controlled trial
Participants	16 patients with leg ulcers of more than 1 year duration Group 1: 8 randomised Group 2: 8 randomised
Interventions	Group 1: breathing sham treatment on the same schedule as HBOT Group 2: HBOT at 2.5 ATA for 90 minutes on 30 occasions over 6 weeks
Outcomes	Ulcer healing Reduction in wound area
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Patients were randomised according to age, but no statement of how randomisation sequence was generated Quote: "The patients were put into two categories according to age and then randomly assigned to two groups."
Allocation concealment (selection bias)	Unclear risk	No statement on allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The gas supply was blinded to all persons involved"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No statement on blinding of outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "All patients went through the 30 treatments"
Incomplete outcome data addressed (use of intention-to-treat (ITT) analysis)	Low risk	Quote: "All patients went through the 30 treatments"
Selective reporting (reporting bias)	Unclear risk	No protocol available, but all outcomes in methods section are reported in results

Kaur 2012

Methods	Randomized, controlled trial. No blinding reported, no sham therapy offered
Participants	30 adult patients with nonhealing ulcer, despite conventional therapy of more than 4 weeks duration Group 1: 15 randomized Group 2: 15 randomized
Interventions	Group 1: Patients received only conventional treatment for management of wounds, i. e., wound debridement, treating infection, daily dressing, which was managed by the referring surgeon Group 2: Patients received conventional treatment plus HBOT for 90 min at 2.5 ATA daily, 6 days a week, a total of 30 sessions
Outcomes	Healed at final follow-up (30 days) Major amputation (30 days) Wound exudate resolved Appearance of granulation tissue Surgical debridement Wound size reduction Transcutaneous oxygen Adverse events (ear pain, claustrophobia, tinnitus, headache)
Notes	Not all diabetic ulcers.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	computer-generated schedule
Allocation concealment (selection bias)	Unclear risk	No statement on allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	No sham therapy offered.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No statement on blinding of outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients completed the study period.
Incomplete outcome data addressed (use of intention-to-treat (ITT) analysis)	Low risk	No patient was excluded from the analysis.
Selective reporting (reporting bias)	Unclear risk	No protocol available, but all outcomes in methods section are reported in results

Kessler 2003

Methods	Randomised controlled trial, no blinding
Participants	28 people with diabetes and Wagner grade I, II and III foot ulcers Group 1: 13 randomised Group 2: 15 randomised All were admitted for care and had transcutaneous oxygen estimated at greater than 30 mmHg
Interventions	Group 1: standard treatment including glycaemic control, offloading and wound care Group 2: in addition, the HBOT group received twice-daily sessions breathing 100% oxygen at 2.5 ATA for 90 minutes for 10 days (total 20 treatments)
Outcomes	Changes in wound surface area Transcutaneous oximetry
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomised according to a randomisation table Quote: "..patients were randomised to standard treatment or standard treatment plus HBO according to a randomisation table."
Allocation concealment (selection bias)	Unclear risk	No statement on allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	No statement on blinding of patients. Since the control group received only conventional treatment and no sham therapy, the patients were unblinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Weekly tracings of the surface area of the ulcer onto griddled transparent film were performed by a physician blinded to the patient's group assignment."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "HBO was well tolerated in all but one patient, who demonstrated a barotraumatic otitis, for which he was discharged from the study."
Incomplete outcome data addressed (use of intention-to-treat (ITT) analysis)	High risk	Quote: "HBO was well tolerated in all but one patient, who demonstrated a barotraumatic otitis, for which he was discharged from the study" Comment: the participant was not included

Kessler 2003 (*Continued*)

		in final analysis.
Selective reporting (reporting bias)	Unclear risk	No protocol available, but all outcomes in methods section are reported in results

Khandelwal 2013

Methods	Randomised, controlled trial, no blinding
Participants	60 participants (35 to 65 years) with type 2 Diabetes mellitus which was adequately controlled. Inclusion criteria were: diabetic foot ulcer of at least 8 weeks duration, patients with only stage III and IV diabetic foot ulcer, absence of vascular insufficiency involving large and medium sized arteries proximal to the ulcer demonstrated by Doppler study, age ≥18 years with type 1 or 2 diabetes Group 1 ("antiseptics"): 20 randomised Group 2 ("HBOT"): 20 randomised Group 3 ("platelet-derived growth factor therapy"): 20 randomised
Interventions	Group 1: patients were surgically debrided and treated with EUSOL, hydrogen peroxide, povidone iodine Group 2: HBO therapy at 2.5 ATA for 60 min per sitting for a total of 30 sittings or till the ulcer healed. These sittings were distributed over a period of 10 weeks. Patients were given either daily or alternate day therapy depending on availability. Occasional wound debridement. No anti-septics were used
Outcomes	Healed at final follow-up (10 weeks) Time to complete healing Mean wound size
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information about the sequence generation process
Allocation concealment (selection bias)	Unclear risk	No statement on allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	No sham therapy offered.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unlikely given the design.

Khandelwal 2013 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	High risk	Incomplete outcome data. No reasons mentioned for loss of patients during follow-up
Incomplete outcome data addressed (use of intention-to-treat (ITT) analysis)	High risk	Probably no intention-to-treat analysis.
Selective reporting (reporting bias)	Unclear risk	No protocol available, but all outcomes in methods section are reported in results

Lin 2001

Methods	Randomised controlled trial. Allocation made after decision to enrol, and patient blinded
Participants	29 people with diabetes and foot lesions Wagner grade 0 to 2
Interventions	Group 1: comparator not specified (sham/no treatment) Group 2: HBOT at 2.5 ATA for 120 minutes daily to 30 treatments
Outcomes	Transcutaneous oxygen
Notes	Abstract only. Ulcers were generally less severe than comparable studies

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "..patients were randomly assigned. ." Comment: patients were randomly assigned, but no details of sequence generation
Allocation concealment (selection bias)	Low risk	Author described information on allocation concealment on request
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No statement on blinding of patients. The comparator was not specified
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No statement on blinding of outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No statement on withdrawals. Numbers at analysis not stated.

Lin 2001 (*Continued*)

Incomplete outcome data addressed (use of intention-to-treat (ITT) analysis)	Unclear risk	Limited information in abstract to make a judgement
Selective reporting (reporting bias)	Unclear risk	Limited information in abstract and supplied to make a judgement

Londahl 2010

Methods	Double-blind, randomised controlled trial with sham HBOT therapy
Participants	94 adults with diabetes and a foot ulcer (below the ankle) for at least 3 months. Wound clinic treatment for at least 2 months and revascularisation not possible or not indicated on vascular assessment Group 1: 45 randomised Group 2: 49 randomised
Interventions	Group 1: sham Group 2: HBOT The study treatment was given as an adjunct to regular treatment at the multidisciplinary diabetic foot clinic. HBOT was delivered at 2.5 ATA for 85 minutes daily from Monday to Friday to a total of 40 treatments over 8 to 10 weeks The sham treatment was the same except the patients breathed air
Outcomes	Complete healing of the index ulcer Case-fatality rate 1 year Major and minor amputation rate Adverse reactions
Notes	An independent steering committee was responsible for the organisation, data-handling and general conduct of the study

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomization was done in blocks of 10" Comment: but no statement of how randomisation sequence was generated
Allocation concealment (selection bias)	Unclear risk	Quote: "using sealed envelopes" Comment: no statement that the envelopes were sequentially numbered and opaque
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Patients from both groups could be treated in the same session as study gases were administered by masks and air or

Londahl 2010 (*Continued*)

		100% oxygen entered the chamber through separate double-blinded pipes"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "A blinded clinical event committee evaluated and classified all reported events as well as clinical outcome."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Numbers and reasons for withdrawal given in study flow chart: HBOT: claustrophobia, 1; hospitalisation, 3; amputation, 1; died, 1; no time, 1; withdrew consent, 1 Placebo: claustrophobia, 1; hospitalisation, 2; amputation, 1; died, 1; no time, 2; withdrew consent, 1
Incomplete outcome data addressed (use of intention-to-treat (ITT) analysis)	Low risk	Quote: "Statistical evaluation was initially performed as an intention-to-treat analysis. " Comment: Per-protocol and ITT analysis presented. ITT analysis included all participants randomised
Selective reporting (reporting bias)	Low risk	Protocol available and pre-specified outcomes are all reported

Ma 2013

Methods	Randomised, controlled trial, no blinding.
Participants	36 patients with diagnosed diabetes, at least one full-thickness wound below the ankle (Wagner grades III or less) for > 3 month, standard care for > 2 month, TcPO2 > 30 mmHg Group 1: 18 randomised Group 2: 18 randomised
Interventions	Group 1: Standard care consisting of offloading, footwear, oral antibiotics, monitoring glucose levels, silver-impregnated dressings, daily debridement and cleaning Group 2: Standard care in addition to HBOT twice daily at 2.5 ATA for 90 minutes, 5 days a week for 2 weeks
Outcomes	Healed at final follow-up (2 weeks) Wound size reduction
Notes	
Risk of bias	

Ma 2013 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation table
Allocation concealment (selection bias)	Unclear risk	Method of concealment was not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	No sham therapy offered
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No statement on blinding of outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The study did not address this issue
Incomplete outcome data addressed (use of intention-to-treat (ITT) analysis)	Unclear risk	The study did not address this issue
Selective reporting (reporting bias)	Unclear risk	No protocol available, but all outcomes in methods section are reported in results

Wang 2011

Methods	Open-label, randomised controlled trial
Participants	86 people with diabetes with 93 chronic non-healing ulcers in the foot area Group 1: 41 randomised (46 ulcers) Group 2: 45 randomised (47 ulcers)
Interventions	Group 1: extracorporeal shockwave therapy (ESWT) Group 2: HBOT EWST treatment dose was ulcer size-dependent. Treatments were conducted 2 times per week for 3 weeks for a total of 6 treatments. After ESWT, patients resumed their initial wound care protocol. Administration of additional antibiotic was discretional HBOT was at a pressure of 2.5 ATA for 90 minutes per treatment daily for a total 20 days of treatments. Patients received the same standard wound care protocol after treatment as ESWT
Outcomes	Ulcers healed Ulcers with $\geq$50% improvement Unchanged ulcers Worsened ulcers

Notes	27 patients (ESWT: 12 with 14 ulcers; HBOT: 15 with 17 ulcers) also received a second course of treatment due to improved but incomplete healing of the ulcers 4 to 6 weeks from the first treatment The denominator used in the analysis was the number of ulcers not patients. Results reported for completers. Clinical trial number NCT01219127	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as randomised, but no statement of how randomisation sequence was generated
Allocation concealment (selection bias)	Unclear risk	No statement on allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "patients and healthcare providers were not blinded"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No statement on blinding of outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "During the course of treatment, 9 patients were excluded including 2 in the ESWT group (2 poor compliance) and seven in the HBO group (7 incomplete follow-up data)."
Incomplete outcome data addressed (use of intention-to-treat (ITT) analysis)	High risk	Patients withdrawing were not balanced in numbers across intervention groups, and reasons were not similar across groups. Analysis not undertaken using ITT
Selective reporting (reporting bias)	Low risk	All outcomes specified in trials register reported in article

ATA: atmospheres absolute
HADS: Hospital Anxiety and Depression Scale
HBOT: hyperbaric oxygen therapy
ITT: intention-to-treat
SF-36: Short Form (36) Health Survey

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

Study	Reason for exclusion
Baroni 1987	Not randomised.
Chin 2001	No appropriate outcome data.
Cruz 2003	Not appropriate wound type.
Deng 2006	All patients received HBOT.
Efrati 2009	All patients received HBOT.
Faglia 1996b	No appropriate outcome data.
Heng 1984	Topical oxygen, not HBOT.
Heng 2000	Topical oxygen, not HBOT.
Holbach 1978	Not randomised or actually dealing with chronic wounds.
Kalani 2000	Not all patients randomised. Authors could not identify randomised subset of the data
Kalani 2002	Not all patients randomised. Authors could not identify randomised subset of the data
Kaya 2009	No RCT
Londahl 2011	Follow up study to the included trial from Londahl 2010. No relevant outcome.
Mathieu 2011	Study protocol not undertaken.
Oriani 1990	Not randomised.
Perrins 1967	Acute burn wound.
Whelan 2001	Animal study.
Zamboni 1997	Not randomised.

HBOT: hyperbaric oxygen therapy

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

O'Reilly 2011

Trial name or title	Hyperbaric Oxygen Therapy (HBOT) for Chronic Diabetic Lower Limb Ulcers
Methods	Randomised controlled trial
Participants	People with diabetes and a non-healing lower limb ulcer
Interventions	Patients allocated to active HBOT receive 90 minutes of oxygen at 2.4 ATA with the patients breathing 100% oxygen when inside the chamber. Those patients randomised to placebo will be compressed on air to 0.3 ATA (10 feet) and kept at that level. The patient will remain in the chamber for the remainder of the placebo treatment breathing normally. At the end of the treatment, after a short period of enhanced ventilation (to simulate surfacing) the chamber will be opened. Patients enter the chambers 5 days per week for approximately 6 weeks for a total of 30 treatments. At the end of the 6-week treatment phase, patients enter a 6-week follow-up phase
Outcomes	The primary outcome in this study is freedom from having, or meeting the criteria for, a major amputation (below knee amputation or metatarsal level) up to 12 weeks after initiation of treatment Wound healing Effectiveness Safety Healthcare resource utilisation Quality of life Cost effectiveness of HBOT
Starting date	April 2008. Estimated completion Jan 2012.
Contact information	Wilhelmine Jones, Reg. Nurse. 1-416-223-6600. willie.jones@uhn.on.ca
Notes	ClinicalTrials.gov Identifier: NCT00621608

Stoekenbroek 2015

Trial name or title	Dutch DAMOCLES multicenter randomized clinical trial
Methods	Multicenter randomized clinical trial, including 30 hospitals and all 10 HBOT centers in the Netherlands. It is planed to enrol 275 patients
Participants	Patients with Types 1 or 2 diabetes, a Wagner 2, 3 or 4 ulcer of the leg present for at least 4 weeks, and concomitant leg ischemia, defined as an ankle systolic blood pressure of <70 mmHg, a toe systolic blood pressure of <50 mmHg or a forefoot transcutaneous oxygen tension (TcpO2) of <40 mmHg. Eligible patients may be candidates for revascularization
Interventions	Patients will be randomly assigned to standard care with or without 40 HBOT-sessions. This regimen consists of forty 90-min treatment sessions at 2.5 ATA. We chose this number of sessions to make sure the HBOT exerts its effect, if any. Patients will breathe 100% oxygen during the session, except for three blocks of 5 min during which ambient air will be administered to prevent oxygen intoxication. Patients will be treated five times per week, once daily, until the ulcer has fully re-epithelialized or until a

Stoekenbroek 2015 (*Continued*)

	maximum of 40 sessions has been reached.
Outcomes	Primary outcome measures are freedom from major amputation after 12 months and achievement of, and time to, complete wound healing. Secondary endpoints include freedom from minor amputations, ulcer recurrence, TcpO2, quality of life, and safety. In addition, we will assess the cost-effectiveness of HBOT for this indication.
Starting date	July 2013
Contact information	Dirk T. Ubbink, Department of Surgery, Room G4-184, Academic Medical Center, P.O. Box 22660, 1100 DD Amsterdam, the Netherlands
Notes	http://www.trialregister.nl; NTR 3944

ATA: atmospheres absolute
HBOT: hyperbaric oxygen therapy

DATA AND ANALYSES

Comparison 1. Diabetic ulcers

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Healed at end of treatment (6 weeks)	5	205	Risk Ratio (M-H, Fixed, 95% CI)	2.35 [1.19, 4.62]
2 Healed at end of treatment. Best-case.	5	216	Risk Ratio (M-H, Fixed, 95% CI)	4.61 [2.35, 9.08]
3 Healed at end of treatment. Worst-case.	5	216	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.51, 1.37]
4 Healed at 6 months	2	112	Risk Ratio (M-H, Fixed, 95% CI)	1.70 [0.90, 3.20]
5 Healed at 6 months. Best-case.	2	112	Risk Ratio (M-H, Fixed, 95% CI)	2.71 [1.53, 4.83]
6 Healed at 6 months. Worst-case.	2	112	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.57, 1.54]
7 Healed at 1 year	3	212	Risk Ratio (M-H, Random, 95% CI)	9.53 [0.44, 207.76]
8 Healed at 1 year. Peto analysis method.	3	212	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.58 [4.33, 13.29]
9 Healed at 1 year. Best-case.	3	212	Risk Ratio (M-H, Random, 95% CI)	10.17 [0.47, 220.48]
10 Healed at 1 year. Worst-case.	3	212	Risk Ratio (M-H, Random, 95% CI)	6.55 [0.42, 101.71]
11 Major amputations	5	312	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.11, 1.18]
11.1 Subgroup (30+ treatments)	4	282	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.07, 2.23]
11.2 Subgroup (< 30 treatments)	1	30	Risk Ratio (M-H, Random, 95% CI)	0.29 [0.07, 1.16]
12 Major amputations. Best-case.	5	312	Risk Ratio (M-H, Fixed, 95% CI)	0.20 [0.10, 0.38]
13 Major amputations. Worst-case.	5	312	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.13, 2.98]
14 Major amputation subgroup by use of sham	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
14.1 Sham HBOT	2	112	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.09, 2.44]
14.2 No sham	3	200	Risk Ratio (M-H, Fixed, 95% CI)	0.15 [0.06, 0.36]
15 Minor amputations	4	242	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.19, 3.10]
16 Minor amputations. Best-case.	4	242	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.17, 1.75]
17 Minor amputations. Worst-case.	4	242	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.21, 4.02]
18 Transcutaneous oxygen tensions change after treatment	1	68	Mean Difference (IV, Fixed, 95% CI)	9.0 [4.68, 13.32]
19 Absolute difference in transcutaneous oxygen at end of treatment	3	113	Mean Difference (IV, Fixed, 95% CI)	11.76 [5.68, 17.84]
20 Ulcer area reduction (%)	2	63	Mean Difference (IV, Random, 95% CI)	18.10 [1.40, 34.79]
21 Quality of life - SF-36 physical summary score	1	33	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-8.58, 8.18]
22 Quality of life - SF-36 mental summary score	1	33	Mean Difference (IV, Fixed, 95% CI)	6.60 [-3.93, 17.13]

Comparison 2. Venous ulcers

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Healed at 18 weeks	1	16	Risk Ratio (M-H, Fixed, 95% CI)	5.0 [0.28, 90.18]
2 Healed at 18 weeks. Best-case.	1	16	Risk Ratio (M-H, Fixed, 95% CI)	9.0 [0.56, 143.89]
3 Healed at 18 weeks. Worst-case.	1	16	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.15, 2.98]
4 Wound size reduction at end treatment (6 weeks)	1	16	Mean Difference (IV, Fixed, 95% CI)	33.0 [18.97, 47.03]
5 Wound size reduction at 18 weeks	1	11	Mean Difference (IV, Fixed, 95% CI)	29.60 [-22.99, 82.19]

Comparison 3. Mixed ulcers types

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Healed at end of treatment (30 days)	1	30	Risk Ratio (M-H, Fixed, 95% CI)	7.0 [0.39, 124.83]
2 Major amputations	1	30	Risk Ratio (M-H, Fixed, 95% CI)	0.2 [0.03, 1.51]
3 Periwound transcutaneous oxygen tensions at the end of treatment	1	30	Mean Difference (IV, Fixed, 95% CI)	12.90 [4.00, 21.80]
4 Ulcer area reduction (%)	1	30	Mean Difference (IV, Fixed, 95% CI)	61.88 [41.91, 81.85]

Analysis 1.1. Comparison 1 Diabetic ulcers, Outcome 1 Healed at end of treatment (6 weeks).

Review: Hyperbaric oxygen therapy for chronic wounds

Comparison: 1 Diabetic ulcers

Outcome: 1 Healed at end of treatment (6 weeks)

Study or subgroup	HBOT n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Abidia 2003	5/9	1/9		12.1 %	5.00 [0.72, 34.73]
Kessler 2003	2/15	0/13		6.5 %	4.38 [0.23, 83.62]
Khandelwal 2013	9/15	6/14		75.1 %	1.40 [0.67, 2.91]
Londahl 2010	3/49	0/45		6.3 %	6.44 [0.34, 121.33]
Ma 2013	0/18	0/18			Not estimable
Total (95% CI)	**106**	**99**		**100.0 %**	**2.35 [1.19, 4.62]**

Total events: 19 (HBOT), 7 (Control)

Heterogeneity: $Chi^2 = 3.12$, df = 3 (P = 0.37); $I^2 = 4\%$

Test for overall effect: Z = 2.46 (P = 0.014)

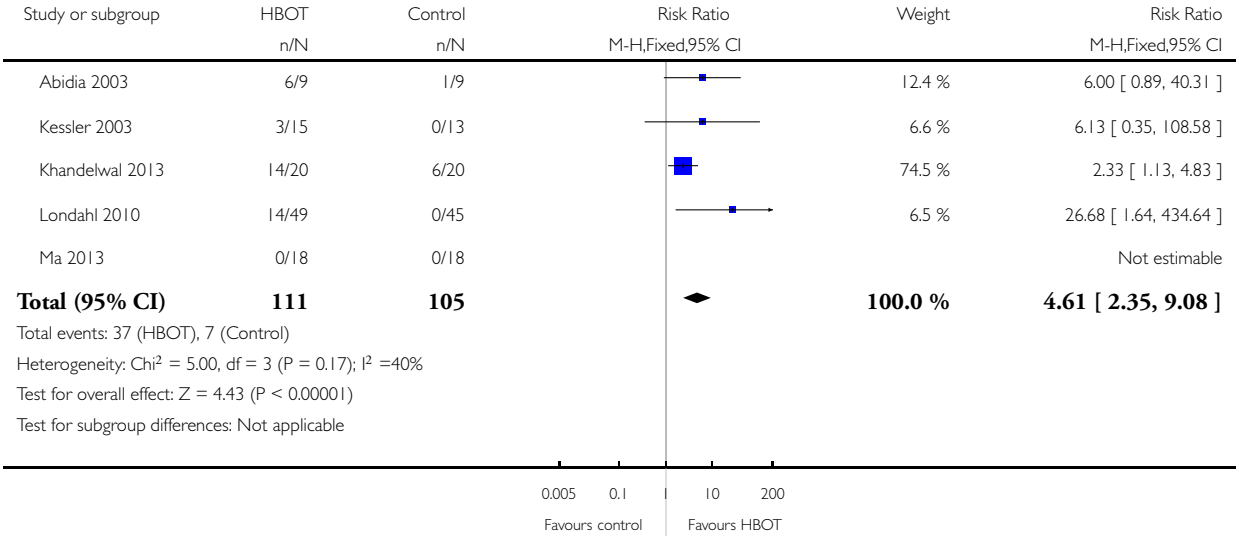
Test for subgroup differences: Not applicable

Analysis 1.2. Comparison 1 Diabetic ulcers, Outcome 2 Healed at end of treatment. Best-case..

Review: Hyperbaric oxygen therapy for chronic wounds

Comparison: 1 Diabetic ulcers

Outcome: 2 Healed at end of treatment. Best-case.



Analysis 1.3. Comparison 1 Diabetic ulcers, Outcome 3 Healed at end of treatment. Worst-case..

Review: Hyperbaric oxygen therapy for chronic wounds

Comparison: 1 Diabetic ulcers

Outcome: 3 Healed at end of treatment. Worst-case.

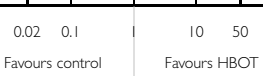
Study or subgroup	HBOT n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Abidia 2003	5/9	2/9		8.9 %	2.50 [0.65, 9.69]
Kessler 2003	2/15	1/13		4.8 %	1.73 [0.18, 16.99]
Khandelwal 2013	9/20	12/20		53.6 %	0.75 [0.41, 1.37]
Londahl 2010	3/49	7/45		32.6 %	0.39 [0.11, 1.43]
Ma 2013	0/18	0/18			Not estimable
Total (95% CI)	**111**	**105**		**100.0 %**	**0.84 [0.51, 1.37]**

Total events: 19 (HBOT), 22 (Control)

Heterogeneity: $Chi^2 = 4.34$, df = 3 (P = 0.23); $I^2 = 31\%$

Test for overall effect: Z = 0.70 (P = 0.48)

Test for subgroup differences: Not applicable



Analysis 1.4. Comparison 1 Diabetic ulcers, Outcome 4 Healed at 6 months.

Review: Hyperbaric oxygen therapy for chronic wounds

Comparison: 1 Diabetic ulcers

Outcome: 4 Healed at 6 months

Study or subgroup	HBOT n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Abidia 2003	5/9	2/9		17.6 %	2.50 [0.65, 9.69]
Londahl 2010	15/49	9/45		82.4 %	1.53 [0.74, 3.15]
Total (95% CI)	**58**	**54**		**100.0 %**	**1.70 [0.90, 3.20]**

Total events: 20 (HBOT), 11 (Control)

Heterogeneity: $Chi^2 = 0.39$, df = 1 (P = 0.53); $I^2 = 0.0\%$

Test for overall effect: Z = 1.64 (P = 0.10)

Test for subgroup differences: Not applicable

Analysis 1.5. Comparison 1 Diabetic ulcers, Outcome 5 Healed at 6 months. Best-case..

Review: Hyperbaric oxygen therapy for chronic wounds

Comparison: 1 Diabetic ulcers

Outcome: 5 Healed at 6 months. Best-case.

Study or subgroup	HBOT n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Abidia 2003	6/9	2/9		17.6 %	3.00 [0.81, 11.08]
Londahl 2010	26/49	9/45		82.4 %	2.65 [1.40, 5.04]
Total (95% CI)	**58**	**54**		**100.0 %**	**2.71 [1.53, 4.83]**

Total events: 32 (HBOT), 11 (Control)

Heterogeneity: $Chi^2 = 0.03$, df = 1 (P = 0.87); $I^2 = 0.0\%$

Test for overall effect: Z = 3.40 (P = 0.00067)

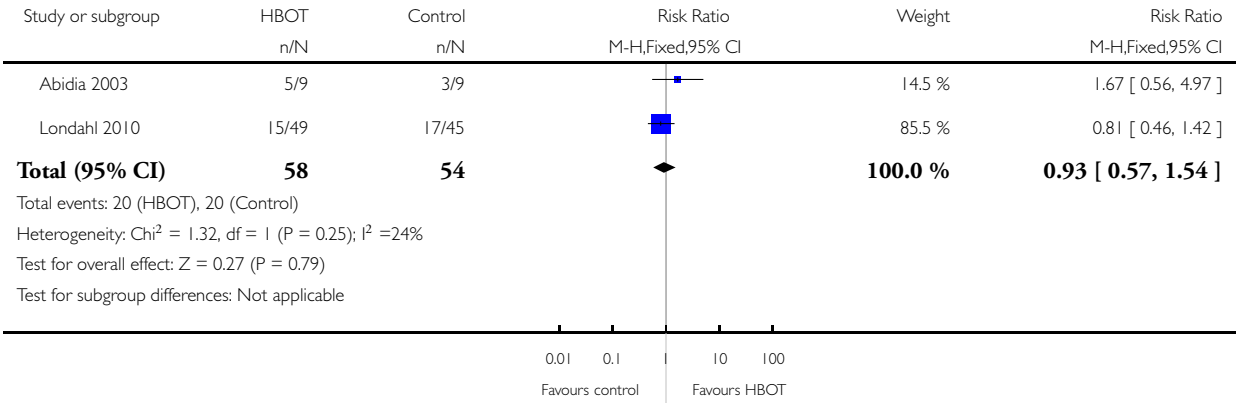
Test for subgroup differences: Not applicable

Analysis 1.6. Comparison 1 Diabetic ulcers, Outcome 6 Healed at 6 months. Worst-case..

Review: Hyperbaric oxygen therapy for chronic wounds

Comparison: 1 Diabetic ulcers

Outcome: 6 Healed at 6 months. Worst-case.

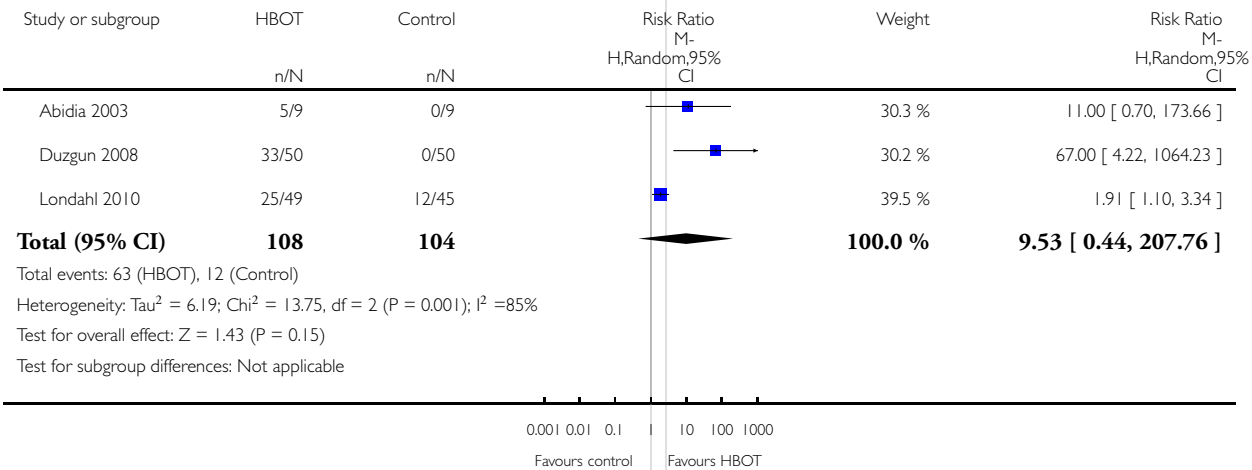


Analysis 1.7. Comparison 1 Diabetic ulcers, Outcome 7 Healed at 1 year.

Review: Hyperbaric oxygen therapy for chronic wounds

Comparison: 1 Diabetic ulcers

Outcome: 7 Healed at 1 year



Analysis 1.8. Comparison 1 Diabetic ulcers, Outcome 8 Healed at 1 year. Peto analysis method..

Review: Hyperbaric oxygen therapy for chronic wounds

Comparison: 1 Diabetic ulcers

Outcome: 8 Healed at 1 year. Peto analysis method.

Study or subgroup	HBOT n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Abidia 2003	5/9	0/9		7.8 %	13.67 [1.84, 101.50]
Duzgun 2008	33/50	0/50		45.8 %	19.21 [8.38, 44.02]
Londahl 2010	25/49	12/45		46.4 %	2.74 [1.20, 6.26]
Total (95% CI)	**108**	**104**		**100.0 %**	**7.58 [4.33, 13.29]**

Total events: 63 (HBOT), 12 (Control)

Heterogeneity: Chi^2 = 11.00, df = 2 (P = 0.004); I^2 =82%

Test for overall effect: Z = 7.08 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 1.9. Comparison 1 Diabetic ulcers, Outcome 9 Healed at 1 year. Best-case..

Review: Hyperbaric oxygen therapy for chronic wounds

Comparison: 1 Diabetic ulcers

Outcome: 9 Healed at 1 year. Best-case.

Study or subgroup	HBOT n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Abidia 2003	6/9	0/9		30.3 %	13.00 [0.84, 201.26]
Duzgun 2008	33/50	0/50		30.2 %	67.00 [4.22, 1064.23]
Londahl 2010	26/49	12/45		39.5 %	1.99 [1.15, 3.45]
Total (95% CI)	**108**	**104**		**100.0 %**	**10.17 [0.47, 220.48]**

Total events: 65 (HBOT), 12 (Control)

Heterogeneity: $Tau^2 = 6.16$; $Chi^2 = 13.81$, df = 2 (P = 0.001); $I^2 = 86\%$

Test for overall effect: Z = 1.48 (P = 0.14)

Test for subgroup differences: Not applicable

Analysis 1.10. Comparison 1 Diabetic ulcers, Outcome 10 Healed at 1 year. Worst-case..

Review: Hyperbaric oxygen therapy for chronic wounds

Comparison: 1 Diabetic ulcers

Outcome: 10 Healed at 1 year. Worst-case.

Study or subgroup	HBOT n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Abidia 2003	5/9	1/9		32.9 %	5.00 [0.72, 34.73]
Duzgun 2008	33/50	0/50		28.1 %	67.00 [4.22, 1064.23]
Londahl 2010	25/49	15/45		38.9 %	1.53 [0.93, 2.51]
Total (95% CI)	**108**	**104**		**100.0 %**	**6.55 [0.42, 101.71]**

Total events: 63 (HBOT), 16 (Control)

Heterogeneity: $Tau^2 = 4.97$; $Chi^2 = 16.10$, df = 2 (P = 0.00032); $I^2 = 88\%$

Test for overall effect: Z = 1.34 (P = 0.18)

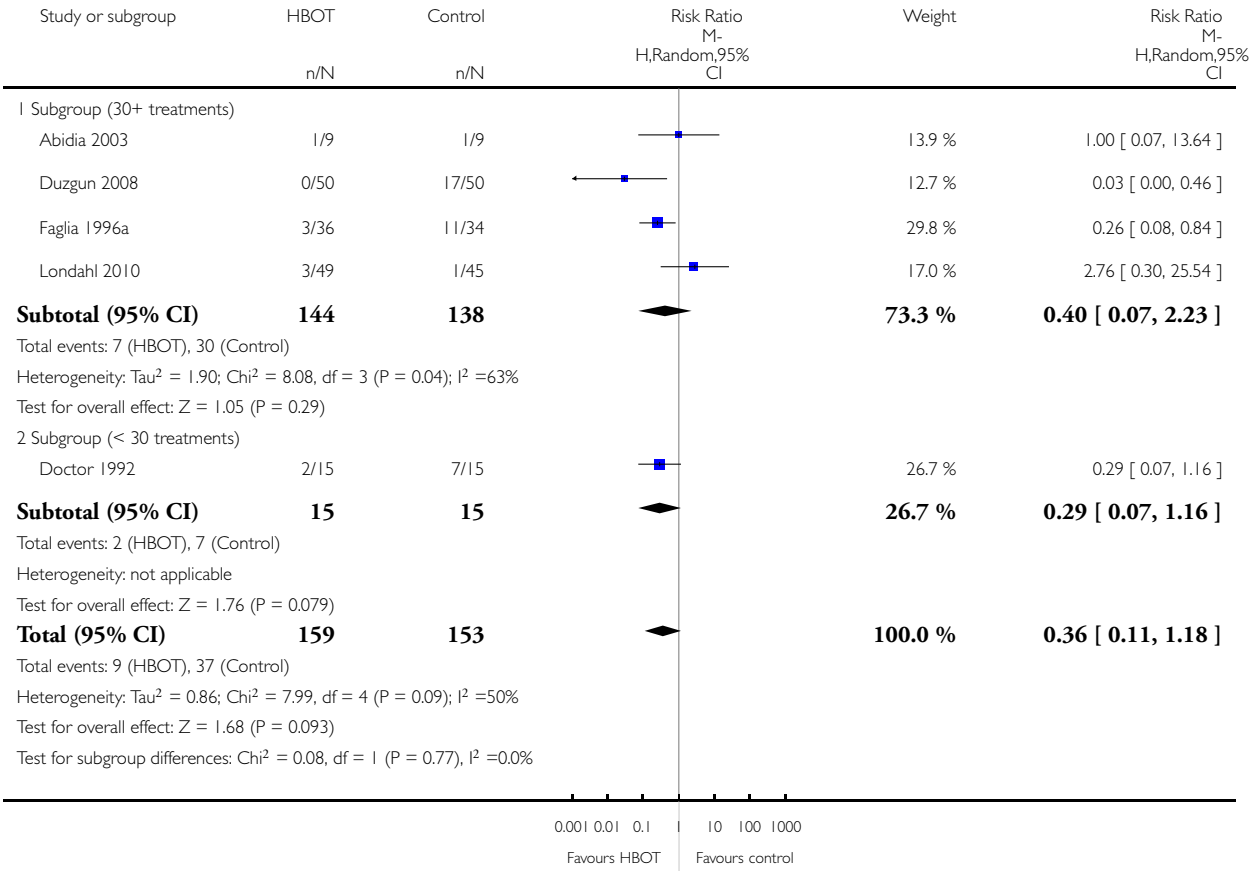
Test for subgroup differences: Not applicable

Analysis 1.11. Comparison 1 Diabetic ulcers, Outcome 11 Major amputations.

Review: Hyperbaric oxygen therapy for chronic wounds

Comparison: 1 Diabetic ulcers

Outcome: 11 Major amputations



Analysis 1.12. Comparison 1 Diabetic ulcers, Outcome 12 Major amputations. Best-case..

Review: Hyperbaric oxygen therapy for chronic wounds

Comparison: 1 Diabetic ulcers

Outcome: 12 Major amputations. Best-case.

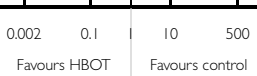
Study or subgroup	HBOT n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Abidia 2003	1/9	2/9		4.2 %	0.50 [0.05, 4.58]
Doctor 1992	2/15	7/15		14.8 %	0.29 [0.07, 1.16]
Duzgun 2008	0/50	17/50		37.1 %	0.03 [0.00, 0.46]
Faglia 1996a	3/36	12/34		26.2 %	0.24 [0.07, 0.76]
Londahl 2010	3/49	8/45		17.7 %	0.34 [0.10, 1.22]
Total (95% CI)	**159**	**153**		**100.0 %**	**0.20 [0.10, 0.38]**

Total events: 9 (HBOT), 46 (Control)

Heterogeneity: $Chi^2 = 3.64$, df = 4 (P = 0.46); $I^2 = 0.0\%$

Test for overall effect: Z = 4.80 (P < 0.00001)

Test for subgroup differences: Not applicable



Analysis 1.13. Comparison 1 Diabetic ulcers, Outcome 13 Major amputations. Worst-case..

Review: Hyperbaric oxygen therapy for chronic wounds

Comparison: 1 Diabetic ulcers

Outcome: 13 Major amputations. Worst-case.

Study or subgroup	HBOT n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Abidia 2003	2/9	1/9		18.0 %	2.00 [0.22, 18.33]
Doctor 1992	2/15	7/15		22.9 %	0.29 [0.07, 1.16]
Duzgun 2008	0/50	17/50		14.9 %	0.03 [0.00, 0.46]
Faglia 1996a	4/36	11/34		24.9 %	0.34 [0.12, 0.98]
Londahl 2010	13/49	1/45		19.3 %	11.94 [1.63, 87.63]
Total (95% CI)	**159**	**153**		**100.0 %**	**0.62 [0.13, 2.98]**

Total events: 21 (HBOT), 37 (Control)

Heterogeneity: $Tau^2 = 2.30$; $Chi^2 = 16.42$, df = 4 (P = 0.003); $I^2 = 76\%$

Test for overall effect: Z = 0.60 (P = 0.55)

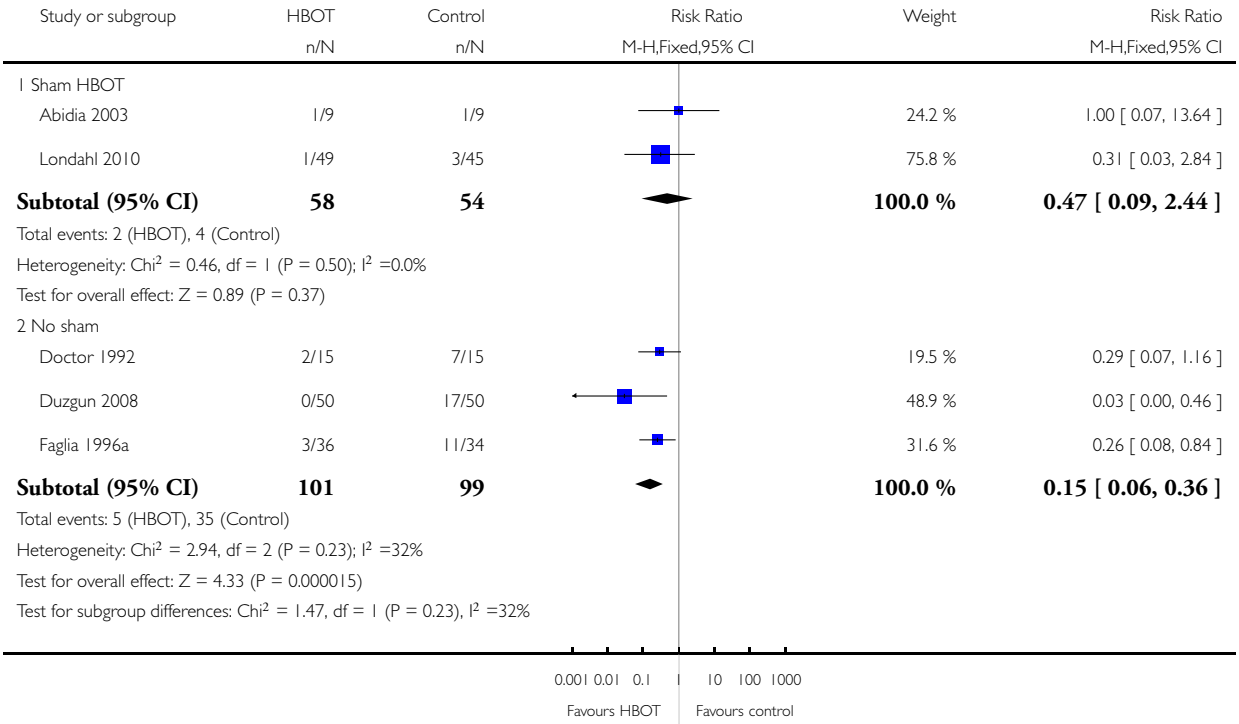
Test for subgroup differences: Not applicable

Analysis 1.14. Comparison 1 Diabetic ulcers, Outcome 14 Major amputation subgroup by use of sham.

Review: Hyperbaric oxygen therapy for chronic wounds

Comparison: 1 Diabetic ulcers

Outcome: 14 Major amputation subgroup by use of sham

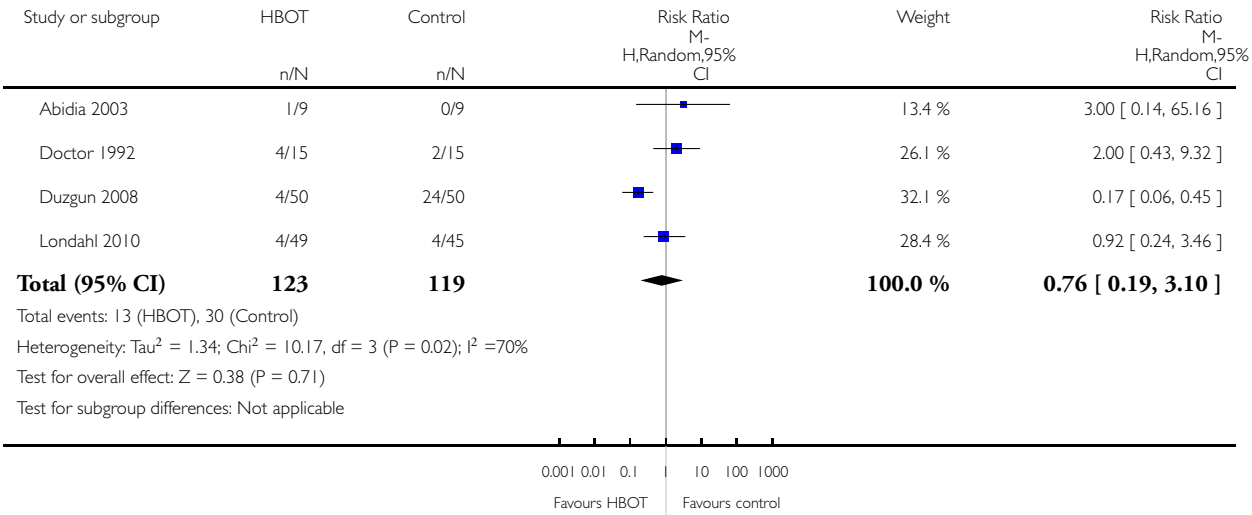


Analysis 1.15. Comparison 1 Diabetic ulcers, Outcome 15 Minor amputations.

Review: Hyperbaric oxygen therapy for chronic wounds

Comparison: 1 Diabetic ulcers

Outcome: 15 Minor amputations



Analysis 1.16. Comparison 1 Diabetic ulcers, Outcome 16 Minor amputations. Best-case..

Review: Hyperbaric oxygen therapy for chronic wounds

Comparison: 1 Diabetic ulcers

Outcome: 16 Minor amputations. Best-case.

Study or subgroup	HBOT n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Abidia 2003	1/9	1/9		13.5 %	1.00 [0.07, 13.64]
Doctor 1992	4/15	2/15		24.3 %	2.00 [0.43, 9.32]
Duzgun 2008	4/50	24/50		32.5 %	0.17 [0.06, 0.45]
Londahl 2010	4/49	7/45		29.8 %	0.52 [0.16, 1.67]
Total (95% CI)	**123**	**119**		**100.0 %**	**0.55 [0.17, 1.75]**

Total events: 13 (HBOT), 34 (Control)

Heterogeneity: $Tau^2 = 0.83$; $Chi^2 = 8.03$, df = 3 (P = 0.05); $I^2 = 63\%$

Test for overall effect: Z = 1.02 (P = 0.31)

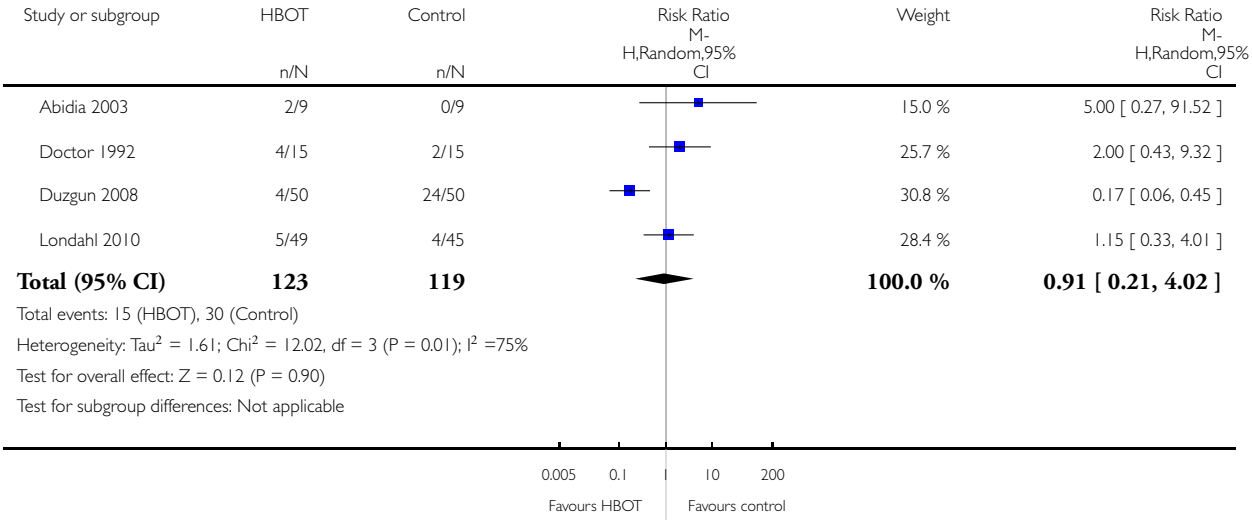
Test for subgroup differences: Not applicable

Analysis 1.17. Comparison 1 Diabetic ulcers, Outcome 17 Minor amputations. Worst-case..

Review: Hyperbaric oxygen therapy for chronic wounds

Comparison: 1 Diabetic ulcers

Outcome: 17 Minor amputations. Worst-case.

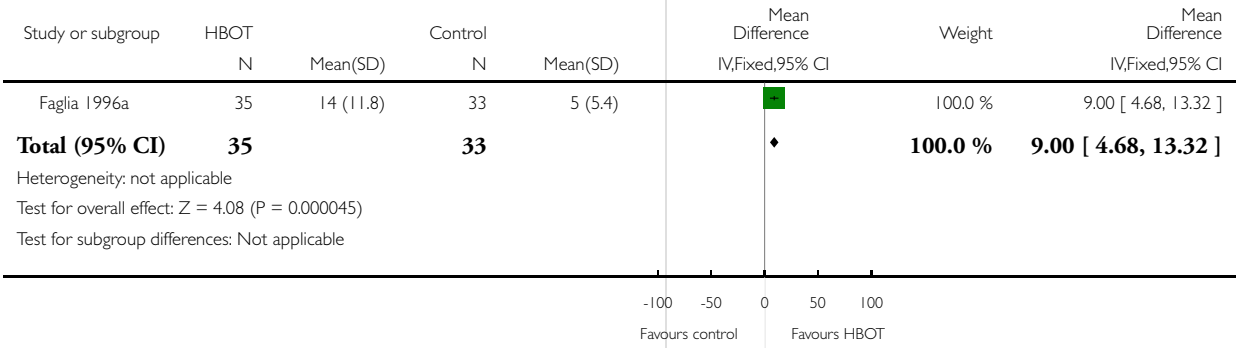


Analysis 1.18. Comparison 1 Diabetic ulcers, Outcome 18 Transcutaneous oxygen tensions change after treatment.

Review: Hyperbaric oxygen therapy for chronic wounds

Comparison: 1 Diabetic ulcers

Outcome: 18 Transcutaneous oxygen tensions change after treatment



Analysis 1.19. Comparison 1 Diabetic ulcers, Outcome 19 Absolute difference in transcutaneous oxygen at end of treatment.

Review: Hyperbaric oxygen therapy for chronic wounds

Comparison: 1 Diabetic ulcers

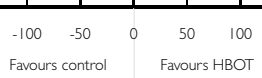
Outcome: 19 Absolute difference in transcutaneous oxygen at end of treatment

Study or subgroup	HBOT N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Abidia 2003	8	49 (19)	8	47 (20)		10.1 %	2.00 [-17.12, 21.12]
Faglia 1996a	35	37.3 (16.1)	33	26.3 (13.5)		74.5 %	11.00 [3.95, 18.05]
Lin 2001	17	57.7 (20.7)	12	35.82 (21.2)		15.4 %	21.88 [6.37, 37.39]
Total (95% CI)	**60**		**53**			**100.0 %**	**11.76 [5.68, 17.84]**

Heterogeneity: $Chi^2 = 2.68$, df = 2 (P = 0.26); $I^2 = 25\%$

Test for overall effect: Z = 3.79 (P = 0.00015)

Test for subgroup differences: Not applicable



Analysis 1.20. Comparison 1 Diabetic ulcers, Outcome 20 Ulcer area reduction (%).

Review: Hyperbaric oxygen therapy for chronic wounds

Comparison: 1 Diabetic ulcers

Outcome: 20 Ulcer area reduction (%)

Study or subgroup	HBOT N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Kessler 2003	14	48.1 (30.3)	13	41.7 (27.3)		34.7 %	6.40 [-15.33, 28.13]
Ma 2013	18	42.4 (20)	18	18.1 (6.5)		65.3 %	24.30 [14.58, 34.02]
Total (95% CI)	**32**		**31**			**100.0 %**	**18.10 [1.40, 34.79]**

Heterogeneity: $Tau^2 = 86.47$; $Chi^2 = 2.17$, df = 1 (P = 0.14); $I^2 = 54\%$

Test for overall effect: Z = 2.12 (P = 0.034)

Test for subgroup differences: Not applicable

Analysis 1.21. Comparison 1 Diabetic ulcers, Outcome 21 Quality of life - SF-36 physical summary score.

Review: Hyperbaric oxygen therapy for chronic wounds

Comparison: 1 Diabetic ulcers

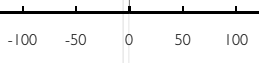
Outcome: 21 Quality of life - SF-36 physical summary score

Study or subgroup	HBOT N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Londahl 2010	23	31.9 (10.8)	10	32.1 (11.5)		100.0 %	-0.20 [-8.58, 8.18]
Total (95% CI)	**23**		**10**			**100.0 %**	**-0.20 [-8.58, 8.18]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.05 (P = 0.96)

Test for subgroup differences: Not applicable



Analysis 1.22. Comparison 1 Diabetic ulcers, Outcome 22 Quality of life - SF-36 mental summary score.

Review: Hyperbaric oxygen therapy for chronic wounds

Comparison: 1 Diabetic ulcers

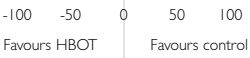
Outcome: 22 Quality of life - SF-36 mental summary score

Study or subgroup	HBOT N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Londahl 2010	23	53.3 (11.8)	10	46.7 (15.1)		100.0 %	6.60 [-3.93, 17.13]
Total (95% CI)	**23**		**10**			**100.0 %**	**6.60 [-3.93, 17.13]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.23 (P = 0.22)

Test for subgroup differences: Not applicable



Analysis 2.1. Comparison 2 Venous ulcers, Outcome 1 Healed at 18 weeks.

Review: Hyperbaric oxygen therapy for chronic wounds

Comparison: 2 Venous ulcers

Outcome: 1 Healed at 18 weeks

Study or subgroup	HBOT n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Hammarlund 1994	2/8	0/8		100.0 %	5.00 [0.28, 90.18]
Total (95% CI)	**8**	**8**		**100.0 %**	**5.00 [0.28, 90.18]**

Total events: 2 (HBOT), 0 (Control)

Heterogeneity: not applicable

Test for overall effect: Z = 1.09 (P = 0.28)

Test for subgroup differences: Not applicable

Analysis 2.2. Comparison 2 Venous ulcers, Outcome 2 Healed at 18 weeks. Best-case..

Review: Hyperbaric oxygen therapy for chronic wounds

Comparison: 2 Venous ulcers

Outcome: 2 Healed at 18 weeks. Best-case.

Study or subgroup	HBOT n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Hammarlund 1994	4/8	0/8		100.0 %	9.00 [0.56, 143.89]
Total (95% CI)	**8**	**8**		**100.0 %**	**9.00 [0.56, 143.89]**
Total events: 4 (HBOT), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.55 (P = 0.12)					
Test for subgroup differences: Not applicable					

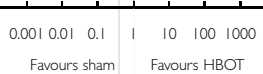
Analysis 2.3. Comparison 2 Venous ulcers, Outcome 3 Healed at 18 weeks. Worst-case..

Review: Hyperbaric oxygen therapy for chronic wounds

Comparison: 2 Venous ulcers

Outcome: 3 Healed at 18 weeks. Worst-case.

Study or subgroup	HBOT n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Hammarlund 1994	2/8	3/8		100.0 %	0.67 [0.15, 2.98]
Total (95% CI)	**8**	**8**		**100.0 %**	**0.67 [0.15, 2.98]**
Total events: 2 (HBOT), 3 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.53 (P = 0.60)					
Test for subgroup differences: Not applicable					



Analysis 2.4. Comparison 2 Venous ulcers, Outcome 4 Wound size reduction at end treatment (6 weeks).

Review: Hyperbaric oxygen therapy for chronic wounds

Comparison: 2 Venous ulcers

Outcome: 4 Wound size reduction at end treatment (6 weeks)

Study or subgroup	HBOT N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Hammarlund 1994	8	35.7 (17)	8	2.7 (11)		100.0 %	33.00 [18.97, 47.03]
Total (95% CI)	**8**		**8**			**100.0 %**	**33.00 [18.97, 47.03]**

Heterogeneity: not applicable

Test for overall effect: Z = 4.61 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 2.5. Comparison 2 Venous ulcers, Outcome 5 Wound size reduction at 18 weeks.

Review: Hyperbaric oxygen therapy for chronic wounds

Comparison: 2 Venous ulcers

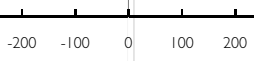
Outcome: 5 Wound size reduction at 18 weeks

Study or subgroup	HBOT N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Hammarlund 1994	6	55.8 (43.1)	5	26.2 (45.3)		100.0 %	29.60 [-22.99, 82.19]
Total (95% CI)	**6**		**5**			**100.0 %**	**29.60 [-22.99, 82.19]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.10 (P = 0.27)

Test for subgroup differences: Not applicable

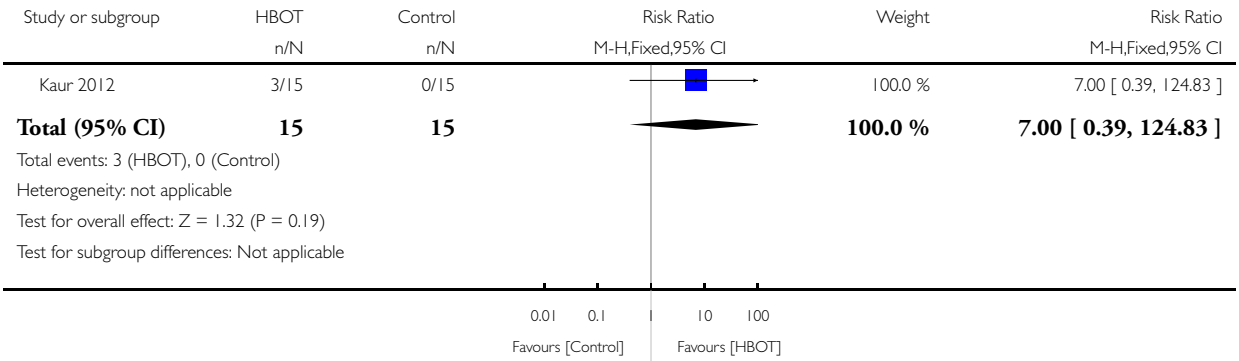


Analysis 3.1. Comparison 3 Mixed ulcers types, Outcome 1 Healed at end of treatment (30 days).

Review: Hyperbaric oxygen therapy for chronic wounds

Comparison: 3 Mixed ulcers types

Outcome: 1 Healed at end of treatment (30 days)

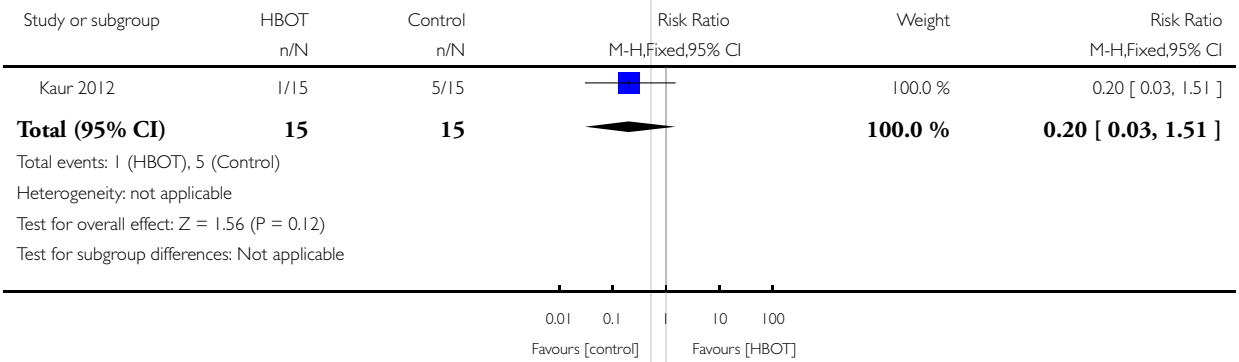


Analysis 3.2. Comparison 3 Mixed ulcers types, Outcome 2 Major amputations.

Review: Hyperbaric oxygen therapy for chronic wounds

Comparison: 3 Mixed ulcers types

Outcome: 2 Major amputations



Analysis 3.3. Comparison 3 Mixed ulcers types, Outcome 3 Periwound transcutaneous oxygen tensions at the end of treatment.

Review: Hyperbaric oxygen therapy for chronic wounds

Comparison: 3 Mixed ulcers types

Outcome: 3 Periwound transcutaneous oxygen tensions at the end of treatment

Study or subgroup	HBOT N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Kaur 2012	15	34.3 (14.8)	15	21.4 (9.5)		100.0 %	12.90 [4.00, 21.80]
Total (95% CI)	**15**		**15**			**100.0 %**	**12.90 [4.00, 21.80]**

Heterogeneity: not applicable

Test for overall effect: Z = 2.84 (P = 0.0045)

Test for subgroup differences: Not applicable

Analysis 3.4. Comparison 3 Mixed ulcers types, Outcome 4 Ulcer area reduction (%).

Review: Hyperbaric oxygen therapy for chronic wounds

Comparison: 3 Mixed ulcers types

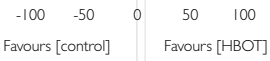
Outcome: 4 Ulcer area reduction (%)

Study or subgroup	HBOT N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Kaur 2012	15	59.27 (36.59)	15	-2.61 (14.77)		100.0 %	61.88 [41.91, 81.85]
Total (95% CI)	**15**		**15**			**100.0 %**	**61.88 [41.91, 81.85]**

Heterogeneity: not applicable

Test for overall effect: Z = 6.07 (P < 0.00001)

Test for subgroup differences: Not applicable



ADDITIONAL TABLES

Table 1. Patients missing from final follow-up

Study	Missing but included	Missing total	Per cent of entered
Khandelwal 2013	0	11	28%
Kaur 2012	0	0	0
Ma 2013	0	0	0
Doctor 1992	0	0	0
Faglia 1996a	0	2	3%
Lin 2001	0	0	0
Abidia 2003	0	2	11%
Hammarlund 1994	0	5	31%
Kessler 2003	0	1	<1%
Duzgun 2008	0	0	0
Londahl 2010	19	19	12% - included in ITT
Wang 2011	0	9	10%

ITT: intention-to-treat

APPENDICES

Appendix 1. Original search methods section 2003 and first update 2012

See: Cochrane Wounds Group search strategy.
Original review:
All publications potentially describing RCTs of therapeutic agents for chronic ulcers were sought from the Specialised Trials Register of the Wounds Group. The Wounds Group Trials Register contains citations of trials identified from searches of 19 electronic databases, including MEDLINE, and EMBASE, and through handsearching journals and conference proceedings.
The Cochrane Central Register of Controlled Trials (CENTRAL) was searched; MEDLINE (1966 to 2003) and EMBASE (1974 to 2003) were also searched.
In addition we made a systematic search for relevant controlled trials in specific hyperbaric literature sources:

1. Experts in the field and leading hyperbaric therapy centres (as identified by personal communication and searching the Internet) were contacted and asked for additional relevant data in terms of published or unpublished randomised trials.
2. Relevant hyperbaric textbooks (Kindwall 1999; Jain 1999; Oriani 1996), journals (Undersea and Hyperbaric Medicine, Hyperbaric Medicine Review, South Pacific Underwater Medicine Society (SPUMS) Journal, European Journal of Hyperbaric

Medicine and Aviation, Space and Environmental Medicine Journal) and conference proceedings (Undersea and Hyperbaric Medical Society, SPUMS, European Undersea and Baromedical Society, International Congress of Hyperbaric Medicine) published since 1980 were handsearched.

3. Authors of relevant studies were contacted to request details of unpublished or ongoing investigations.

4. Database of randomised controlled trials in hyperbaric medicine was searched (DORCTHIM, Bennett 2003). We used the specific search terms "hyperbaric oxygenation", "wounds and injuries", "ulcer", "skin ulcer", "diabetic foot", "varicose ulcer" and "foot ulcer".

First update searches:

The Cochrane Wounds Group Specialised Register (searched January 12 2012);
The Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2011, Issue 4);
Ovid MEDLINE (1950 to January Week 1 2012);
Ovid MEDLINE (In-Process & Other Non-Indexed Citations, January 11, 2012);
Ovid EMBASE (1980 to 2012 Week 01);
EBSCO CINAHL (1982 to January 6 2012).

Appendix 2. Ovid MEDLINE search strategy

1 exp Chronic Disease/
2 exp Wound Healing/
3 and/1-2
4 exp Skin Ulcer/
5 exp Diabetic Foot/
6 (skin ulcer$ or foot ulcer$ or diabetic foot or varicose ulcer$ or venous ulcer$ or leg ulcer$ or stasis ulcer$ or arterial ulcer$ or (lower extremit$ adj ulcer$) or crural ulcer$ or ulcus cruris).ti,ab.
7 ((ischaemic or ischemic) adj (wound$ or ulcer$)).ti,ab.
8 (bed sore$ or pressure sore$ or pressure ulcer$ or decubitus ulcer$).ti,ab.
9 chronic wound$.ti,ab.
10 (chronic adj3 ulcer$).ti,ab.
11 or/3-10
12 exp Hyperbaric Oxygenation/
13 (hyperbar$ adj oxygen$).ti,ab.
14 high pressure oxygen$.ti,ab.
15 oxygen.ti.
16 or/12-15

Appendix 3. Ovid EMBASE search strategy

1 exp Chronic Wound/
2 exp Skin Ulcer/
3 exp Diabetic Foot/
4 (skin ulcer$ or foot ulcer$ or diabetic foot or varicose ulcer$ or venous ulcer$ or leg ulcer$ or stasis ulcer$ or arterial ulcer$ or (lower extremit$ adj ulcer$) or crural ulcer$ or ulcus cruris).ti,ab.
5 ((ischaemic or ischemic) adj (wound$ or ulcer$)).ti,ab.
6 (bed sore$ or pressure sore$ or pressure ulcer$ or decubitus ulcer$).ti,ab.
7 chronic wound$.ti,ab.
8 (chronic adj3 ulcer$).ti,ab.
9 or/1-8
10 exp hyperbaric oxygen/
11 (hyperbar$ adj oxygen$).ti,ab.
12 high pressure oxygen$.ti,ab.
13 oxygen.ti.
14 or/10-13

15 9 and 14

Appendix 4. EBSCO CINAHL search strategy

S14 S8 and S13
S13 (S9 or S10 or S11 or S12)
S12 TI oxygen
S11 TI high pressure oxygen or AB high pressure oxygen
S10 TI hyperbar* oxygen* or AB hyperbar* oxygen*
S9 (MH "Hyperbaric Oxygenation")
S8 S1 or S2 or S3 or S4 or S5 or S6 or S7
S7 TI (chronic wound* or chronic ulcer*) or AB (chronic wound* or chronic ulcer*)
S6 TI (bed sore* or pressure sore* or pressure ulcer* or decubitus) or AB (bed sore* or pressure sore* or pressure ulcer* or decubitus)
S5 AB skin ulcer* or foot ulcer* or diabetic foot* or diabetic feet or leg ulcer* or varicose ulcer* or venous ulcer* or stasis ulcer* or arterial ulcer* or ischemic ulcer* or ischaemic ulcer* or lower extremit*
S4 TI skin ulcer* or foot ulcer* or diabetic foot* or diabetic feet or leg ulcer* or varicose ulcer* or venous ulcer* or stasis ulcer* or arterial ulcer* or ischemic ulcer* or ischaemic ulcer* or lower extremit*
S3 (MH "Diabetic Foot")
S2 (MH "Skin Ulcer+")
S1 (MH "Wounds, Chronic")

WHAT'S NEW

Last assessed as up-to-date: 18 February 2015.

Date	Event	Description
18 February 2015	New search has been performed	Second update, new search, three trials added (Kaur 2012; Khandelwal 2013; Ma 2013). We created a "mixed ulcers group" including trials with patients suffered from diabetic and venous ulcers. "Risk of bias assessment" and "Summary of findings" table completed
18 February 2015	New citation required but conclusions have not changed	New author added to review team.

HISTORY

Protocol first published: Issue 2, 2003

Review first published: Issue 2, 2004

Date	Event	Description
12 January 2012	New search has been performed	First update, new search, four trials added (Duzgun 2008; Kessler 2003; Londahl 2010; Wang 2011). 'Risk of bias' assessment and 'Summary of findings' table completed
12 January 2012	New citation required and conclusions have changed	New author added to review team.
7 November 2008	Amended	Converted to new review format.
14 October 2003	New citation required and conclusions have changed	Substantive amendment.

CONTRIBUTIONS OF AUTHORS

P. Kranke: initiated the study, dealt with correspondence, developed the protocol, undertook the searching and selected studies, appraised and data abstracted studies, entered data and wrote the review and participated in the update of the review.

M. Bennett: developed and edited the protocol, undertook the searching and selected studies, appraised and data abstracted studies, undertook the statistical analysis and wrote the review and the updated review.

M. Martyn-St James: appraised and data abstracted selected studies identified for the update, and undertook the statistical and narrative synthesis for the update.

S. Debus: commented on the protocol and the review.

A. Schnabel: appraised and data abstracted studies, contributed to discussion.

S. Weibel: appraised and data abstracted selected studies, and undertook the statistical and narrative synthesis for the second update.

Contributions of editorial base:

Nicky Cullum: edited the review, advised on methodology, interpretation and review content. Approved the final review and review update prior to submission.
Sally Bell-Syer: coordinated the editorial process. Advised on methodology, interpretation and content. Edited the review and the updated reviews.
Ruth Foxlee: designed the search strategy, ran the searches and edited the search methods section for the update.
Amanda Briant: ran the searches for the second update.

DECLARATIONS OF INTEREST

Michael Bennett is a salaried hyperbaric physician working in a State-funded institution where he treats participants with chronic wounds from a variety of causes. Part of his entitlement in that position is reimbursement for attendance at appropriate scientific meetings.

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Internal sources

- Departmental sources from the Department of Anaesthesiology, University of Wuerzburg, Germany, Germany.

External sources

- This project was supported by the National Institute for Health Research, via Cochrane Infrastructure funding to Cochrane Wounds. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health, UK.
- NIHR Programme Grants for Applied Research, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In this update, we identified one trial (Kaur 2012) which enrolled patients with different co-morbidities and therefore different types of ulcers. Due to the possibility that in future more studies of this types will be found, we decided to add this as a new comparison termed “mixed ulcers types” to the analysis.

We introduced some changes within the methodological quality assessment (performance bias). In the original review, we defined “unclear risk of bias” for “blinding of participants and personnel”, when the study does not specify the blinding process independent of the described treatment of the control group (e.g. no sham therapy offered) . We reconsidered this point and judged to assess studies as “high risk of bias”, when they offered no sham therapy to the patients of the control arm. Therefore, Doctor 1992; Duzgun 2008; Faglia 1996a; Kessler 2003 are now assessed as “high risk of performance bias”.

INDEX TERMS

Medical Subject Headings (MeSH)

*Wound Healing; Amputation [utilization]; Chronic Disease; Diabetic Foot [*therapy]; Hyperbaric Oxygenation [adverse effects]; Randomized Controlled Trials as Topic; Varicose Ulcer [*therapy]

MeSH check words

Humans