Hyperbaric oxygen therapy for chronic wounds (Review)

Kranke P, Bennett MH, Debus SE, Roeckl-Wiedmann I, Schnabel A

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TABLE OF CONTENTS

[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. The wide range of therapeutic strategies for such wounds reflects the various pathologies that 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 (diabetic foot ulcers, venous and arterial ulcers and pressure ulcers).

Search methods

We searched the Cochrane Wounds Group Specialised Trial Register (searched 6 February 2003), CENTRAL (The Cochrane Library Issue 1, 2003), Medline (1966 - 2003), EMBASE (1974 - 2003), DORCTHIM (1996 - 2003), and reference lists of articles. Relevant journals were handsearched and researchers in the field were contacted.

Selection criteria

Randomised studies 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 reviewers independently evaluated the quality of the relevant trials using the validated Oxford-Scale (Jadad 1996) and extracted the data from the included trials.

Main results

Five trials contributed to this review. Diabetic foot ulcer (4 trials, 147 patients): Pooled data of three trials with 118 patients showed a reduction in the risk of major amputation when adjunctive HBOT was used, compared to the alternative therapy (RR 0.31, 95% CI 0.13 to 0.71). Sensitivity analysis for the allocation of dropouts did not significantly alter that result. This analysis predicts that we would need to treat 4 individuals with HBOT in order to prevent 1 amputation in the short term (NNT 4, 95% CI 3 to 11). There was no statistically significant difference in minor amputation rate (pooled data of two trials with 48 patients). Healing rates were reported in one trial (Abidia 2003) which showed a significant improvement in the chance of healing 1 year after therapy (RR for failure to heal with sham 2.3, 95%CI 1.1 to 4.7, P=0.03), although no effect was determined immediately post HBOT, nor at 6 months. Further, the beneficial effect after 1 year was sensitive to allocation of dropouts.

Venous ulcer: (1 trial, 16 patients): This trial reported data at six weeks (wound size reduction) and 18 weeks (wound size reduction and healing rate) and suggested a significant benefit of HBOT in terms of reduction in ulcer area only at 6 weeks (WMD 33%, 95%CI 19% to 47%, P<0.00001).

Arterial and pressure ulcers: No trials that satisfied inclusion criteria were located.

Authors' conclusions

In people with foot ulcers due to diabetes, HBOT significantly reduced the risk of major amputation and may improve the chance of healing at 1 year. The application of HBOT to these patients may be justified where HBOT facilities are available, however economic evaluations should be undertaken. In view of the modest number of patients, methodological shortcomings and poor reporting, this result should be interpreted cautiously however, and an appropriately powered trial of high methodological rigour is justified to verify this finding and further define those patients who can be expected to derive most benefit from HBOT.

Regarding the effect of HBOT on chronic wounds associated with other pathologies, any benefit from HBOT will need to be examined in further, rigorous randomised trials. The routine management of such wounds with HBOT is not justified by the evidence in this review.

PLAIN LANGUAGE SUMMARY

Hyperbaric oxygen therapy for treating chronic wounds

Chronic wounds, often associated with diabetes, arterial or venous disease are common and have a high impact on the well-being 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 measures to treat them. HBOT involves people breathing pure oxygen in a specially designed chamber (such as that used for deep sea divers suffering pressure problems after resurfacing).

The review of trials found that HBOT seems to reduce the number of major amputations in people with diabetes who have chronic foot ulcers, and may reduce the size of wounds caused by disease to the veins of the leg, but found no evidence to confirm or refute any effect on other wounds caused by lack of blood supply through the arteries or pressure ulcers.

BACKGROUND

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 im-

prove ischaemia in the limb in order to promote healing, perhaps through bypass surgery when technically possible (Leng 2002). In ulcers associated with venous insufficiency, on the other hand, compression bandaging is likely to be more appropriate (Cullum 2002). 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).

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 from a variety of sources. It has been estimated that 1% of the population of industrialised countries will experience a leg ulcer at some time (Baker 1991). While most leg ulcers will be the result of venous insufficiency, about 25% are likely to be arterial (Cullum 2002, Andersson 1993). Wound care in the UK costs in excess of £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 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, suledoxide) 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). There are many others. In practice, wound management is often a sequential and fruitless 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 15% experience foot ulceration and in whom the amputation rate is 15 - 70 times that in the general population (Calman 1998; SIGN 1997).

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 0.25-1.8% (Veves 1992; Lee 1993; Apelqvist 1993; Humphrey 1996). Ulcer care is responsible for a large proportion of the cost of healthcare for people with diabetes. The relapse rate for diabetic foot ulcers is 66% over 5 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. 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 UKP 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 ulcers

Pressure ulcers (also known as pressure sores, decubitus ulcers and bed sores) may present as persistently hyperaemic, 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). Pressure sores can be viewed as typical complications in all healthcare settings with a prevalence of 6-10% in National Health Services hospitals in the UK (O'Dea 1999).

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.

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, Dimitrijevich 1999, Cianci 1993, Bayati 1998, Zhao 1994, Rabkin 1988, Stevens 1993).

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 1 to 2 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 1ATA for 90 minutes daily) and hyperbaric oxygen (100% oxygen at 2.4ATA 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 revascularization of irradiated tissue than air-breathing controls ($p = 0.89$). Hyperbaric oxygen demonstrated an eight- to ninefold increased vascular density over both normobaric oxygen and air-breathing controls ($p = 0.001$).

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 patients.

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. 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 that compare the effect on chronic wound healing of treatment with HBOT with no HBOT. Studies were considered irrespective of allocation concealment or blinding status.

Types of participants

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

Types of interventions

We compared wound care regimens which included HBOT with similar regimens that excluded HBOT. Where co-interventions differed significantly between studies this was clearly stated and the implications discussed.
HBOT administered in a compression chamber between pressures of 1.5ATA and 3.0ATA 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 (see background). The salient feature of the comparison group was that these measures had failed before enrolment in the studies. Subgroup analysis was planned to evaluate the impact of different comparator strategies.

Types of outcome measures

Studies were eligible for inclusion if they reported any of the following outcome measures:
1. Diabetic ulcers.
Primary outcome measures: proportion of ulcers healed and proportion undergoing major amputation (defined as amputation of the lower or upper extremity above the ankle or the wrist, respectively).
Secondary outcome measures: 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.
2. Venous ulcers.
Primary outcome measure: proportion of ulcers healed.
Secondary outcome measures: time to complete healing, wound size reduction, quality of life, pain and recurrence rate.
3. Arterial ulcers.
Primary outcome: proportion of ulcers healed, proportion undergoing major amputation.
Secondary outcomes: time to complete healing, proportion undergoing minor amputation, pain reduction, quality of life and recurrence rate.
4. Pressure ulcers.
Primary outcome measure: proportion of ulcers healed.
Secondary outcome measures: time to complete healing, wound size reduction, quality of life and recurrence rate.
5. Adverse events of HBOT.
Proportion of patients with visual disturbance (short and long-term), barotrauma (aural, sinus, pulmonary in the short and long-term) and oxygen toxicity (short-term) with respect to HBOT obtained from the included studies. We also examined the proportion of patients withdrawn from treatment for any reason and planned to relate such withdrawals to the frequency and dose of HBOT where possible. Any other recorded adverse effects were to be reported and discussed.

Search methods for identification of studies

It was our intention to capture both published and unpublished studies.
See: Cochrane Wounds Group search strategy.
All publications potentially describing RCTs of therapeutic agents for chronic ulcers were sought from the Specialised Trials Register of the Wounds Group (search dates 6 February 2003). The

Wounds Group Trials Register contains citations of trials identified from searches of 19 electronic databases, including Medline, Cinahl and EMBASE, and through handsearching journals and conference proceedings.
The Cochrane Central Register of Controlled Trials (CENTRAL) was searched (Issue 1, 2003) using the following search strategy:
1. WOUNDS AND INJURIES explode all trees (MeSH)
2. ULCER explode all trees (MeSH)
3. SKIN ULCER explode all trees (MeSH)
4. FOOT ULCER explode all trees (MeSH)
5. LEG ULCER explode all trees (MeSH)
6. VARICOSE ULCER explode all trees (MeSH)
7. VENOUS ULCER explode all trees (MeSH)
8. DIABETIC FOOT explode all trees (MeSH)
9. (leg near ulcer*) or (foot near ulcer*)
10. (skin near ulcer*) or (diabetic near foot)
11. ((skin near wound*) or (skin near burn*)
12. ((varicose near ulcer*) or (venous near ulcer*)
13. (chronic near ulcer*) or (stasis near ulcer*)
14. (diabetic near ulcer*) or (arterial near ulcer)
15. ((chronic near wound*) or (stasis near wound*)
16. (arterial near wound*) or (diabetic near wound*)
17. ((plantar near ulcer*) or (heel near ulcer*)
18. ((leg near injur*) or (foot near injur*)
19. (bed next sore)
20. (decubitus near ulcer*) or (pressure near ulcer*)
21. (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11)
22. (#12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20)
23. (#21 or #22)
24. HYPERBARIC OXYGENATION explode all trees (MeSH)
25. (hyperbar* next oxygen*)
26. (high near pressure near oxygen*)
27. oxygen*:ti
28. (#24 or #25 or #26 or #27)
29. (#23 and #28)
Medline (1966 - 2003) and EMBASE (1974 - 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”.

All languages were considered. Authors were contacted to discuss any ambiguity about the published data.

Data collection and analysis

Data retrieval and management:
One reviewer (MB) was responsible for handsearching and identification of appropriate studies for consideration. Three reviewers (PK, MB and IR) independently examined the electronic search results and identified potentially relevant studies which were entered into a bibliographic software package (Reference Manager) irrespective of whether one or more reviewers identified the study. All comparative clinical trials identified and judged to be potentially relevant were retrieved in full and reviewed independently by three reviewers, 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 reviewers (MB, IR) have expertise in clinical epidemiology.
Data extraction:
Using the data extraction form developed for this review, each reviewer extracted relevant data, graded the studies for methodological quality using the validated three-item, five-point Oxford-Scale (Jadad 1996), and made a recommendation for inclusion or exclusion from the review. The method of Jadad scores trials on three criteria (randomisation, double-blinding and description of withdrawals), each of which, if present, is given a score of 1. Further points are available for description of a reliable randomisation method and use of a placebo (modified for our analysis to include a sham HBOT session). The scores are totalled as an estimate of overall quality of reporting. Any differences were settled by consensus. All data extracted reflected original allocation group where possible to allow an intention to treat analysis. Losses to follow up were identified where this information is given.
Analyses:
Analysis was grouped by wound aetiology. If required, a further group where aetiology was unclear was planned. For proportions (dichotomous outcomes), Relative Risk (RR) was used. We used a fixed-effects model where there was no evidence of significant heterogeneity between studies (see below), and planned to employ a random effects model when such heterogeneity was likely.
1. Proportion of wounds healed. Dichotomous outcome. The RR for healing with HBOT was established using the intention to

treat data of the HBOT versus the control group. Analyses were performed with RevMan 4.2 software. As an estimate of the statistical significance of a difference between experimental interventions and control interventions we calculated RR for benefit using HBOT with 95% confidence intervals (CI). A statistically significant difference between experimental intervention and control intervention was assumed if the 95% CI of the RR did not include the value 1.0. As an estimate of the clinical relevance of any difference between experimental intervention and control intervention we calculated the number-needed-to-treat (NNT) and number-needed-to-harm (NNH) with 95% CI as appropriate.

2. Proportion of those requiring amputation. The RR for amputation with and without HBOT was calculated using the methods described in (1) above.

3. Reduction in wound area. The weighted mean differences (WMD) in wound size before and after treatment was compared between the HBOT and control groups using RevMan 4.2. The combined WMD between the groups was calculated and a statistically significant difference was defined as existing if the 95% CI did not include a zero WMD.

4. Pain scores. WMD in pain scores were calculated in a way analogous to that described in (3) above.

5. QOL. Statistical method employed depended on the nature of the data presented in the relevant papers.

6. Proportion suffering recurrence. The RR for recurrence with or without HBOT as described in (1) above.

7. Time to complete healing. WMD in time to complete healing between the HBOT and control groups was calculated in a method analogous to (3) above.

8. Dichotomous data was considered for adverse events (number of patients with adverse events versus number of patients without them in both groups) in the HBOT groups of the included studies.

Sensitivity analyses:

We intended to perform sensitivity analyses for missing data and study quality.

Missing data

We planned to employ sensitivity analyses using different approaches to imputing missing data. The best-case scenario assumes that none of the originally enrolled patients missing from the primary analysis in the treatment group had the negative outcome of interest whilst all those missing from the control group did. The worst-case scenario is the reverse.

Study quality

If appropriate we planned to conduct a sensitivity analysis by study quality based on the Jadad score and an assessment of adequate sample size to detect the clinically important difference in outcome for which the study was designed.

Baseline risk

Since the obtained NNTs or NNHs differ depending on the underlying risk for an event in the study population, subgroup analyses due to different baseline risks was considered. In which case we planned to use "truncated" data restricting the analyses to a predefined control event rate.

Subgroups:

Where appropriate data exist, we considered subgroup analysis based on:

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.

Heterogeneity was explored and subgroup analyses performed when appropriate. Statistical heterogeneity was assumed to be significant if the I^2 analysis suggested more than 30% of the variability in an analysis was due to differences between trials. Consideration was then given to the appropriateness of pooling and meta-analysis.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

We identified 26 publications dealing with the treatment of chronic wounds with adjunctive HBOT (MEDLINE 14, reference lists of identified articles 5, DORCTHIM 3, handsearching 3, personal communication 1). Initial examination suggested 20 possible comparative trials where systemic hyperbaric oxygen was employed in at least one arm of the study. After appraisal of the full report for each trial, we excluded 13 publications: 6 where allocation was not random (Holbach 1978; Baroni 1987; Oriani 1990; Zamboni 1997; Kalani 2000; Kalani 2002), 2 where the intervention of interest was topically applied oxygen (Heng 1984; Heng 2000), 1 dealing with acute burn wounds (Perrins 1967), and 1 which was an animal study (Whelan 2001). 3 of the remaining reports were excluded as contributing no appropriate outcome data (Faglia 1996a; Abidia 2001c; Chin 2001). An approach to the authors did not produce further data. (See Table of Excluded Studies).

In total, 5 trials contributed to this review and these were published between 1992 (Doctor 1992) and 2003 (Abidia 2003). The reviewers are unaware of any ongoing RCTs in the area except those mentioned in the appropriate section of the review. In total, these trials include data on 163 patients, 85 receiving HBOT and 78 a control treatment, and the largest (Faglia 1996b) accounts for 43% of cases. In the report of Doctor (Doctor 1992), the number of patients 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), while the other 4 included patients with diabetic ulcers. (See Table of Included Studies).

Diabetic foot ulcers

The treatment pressure and time schedule used for delivery of oxygen varied between studies. Doctor (Doctor 1992) used 3.0ATA for 45 minutes, while the remainder used between 2.2 and 2.5 ATA for between 90 and 120 minutes. Four trials gave between 30 and 38 sessions once daily either 5 or 6 days each week, over a 6 weeks period, whilst one trial (Doctor 1992), unusually applied 4 sessions only, over a period of 2 weeks. Two trials (Abidia 2003; Lin 2001) employed a sham treatment in the control group, on the same schedule as the HBOT group. The other 2 trials did not employ a sham therapy (Doctor 1992; Faglia 1996b).

Inclusion criteria varied in these trials. Doctor 1992 included any person with diabetes with a chronic foot lesion (time not specified); Faglia 1996b included people with diabetes and Wagner grade 2, 3 or 4 lesions (Wagner 1987); Lin 2001 patients with "early diabetic feet", Wagner grades 0,1 or 2, and Abidia 2003 included people with diabetes whose lesions had been present for more than 6 weeks and were between 1 and 10 cm in diameter. Exclusion criteria generally followed from the specific inclusions detailed above, but Abidia 2003 also specifically excluded patients for whom vascular surgical procedures were planned. While the recruitment period for one study (Lin 2001) was not stated, all other trials recruited patients over a 2 year period in which conventional treatment had failed.

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), 2 trials described a comprehensive and specialised multidisciplinary wound management program to which HBOT was added for the active arm of the trial (Faglia 1996; Abidia 2003), and 1 specified a surgical and dressing regimen common to both arms (Doctor 1992).

The follow-up periods varied between trials. 1 trial reported data immediately following the course of therapy (Lin 2001), 2 trials followed patients to discharge from hospital (Doctor 1992; Faglia 1996b), and 1 gave results at 1 year (Abidia 2003). All included studies 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 1 year (Abidia 2003), vascular responsiveness (Abidia 2003) and laser-Doppler perfusion scans (Lin 2001).

Venous ulcers

Hammarlund 1994 used a treatment session of 2.4ATA for 90 minutes to a total of 30 sessions over 6 weeks, and employed an air breathing sham treatment on the same schedule. On this trial, patients were required to have persistent venous ulcers for more than 1 year with arterial blood pressures at the ankle and great toe within the normal range when compared 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. Patients were excluded if they were currently smoking or had chronic illnesses such as diabetes or connective tissue disorders. The recruitment period for this study is not known, but was over more than 1 year. The comparator treatment was not specified. The patients were followed up to 18 weeks from enrolment and data was obtained on wound area and the presence or absence of complete healing.

Risk of bias in included studies

OXFORD-SCALE (Jadad Score)

Diabetic ulcers.

Study quality was variable across these trials. Two of the 4 included studies were assigned a score of 2, reflecting the lack of blinding or use of a sham therapy (Doctor 1992; Faglia 1996), while the other 2 studies 4 (Lin 2001) and 5 respectively (Abidia 2003).

Venous ulcers.

The single trial scored 4 (Hammarlund 1994).

RANDOMISATION

Diabetic ulcers.

Allocation concealment was adequately described in only 1 of the 4 trials(Abidia 2003), whilst Lin 2001 supplied further information confirming allocation after enrolment. Whether allocation was concealed remained unclear in the remaining 2 studies in which randomisation procedures were loosely described, if at all.

Venous ulcers.

In the single trial dealing with venous ulcers, randomisation and allocation concealment was adequately described (Hammarlund 1994).

PATIENT BASELINE CHARACTERISTICS

Diabetic ulcers.

The baseline characteristics of patients entering these trials varied. 2 trials measured and reported Wagner Grades of the ulcers at baseline (Wagner 1987), but included different subsets of patients. Faglia 1996b included people with Wagner grade 2, 3 or 4 lesions, whilst Lin 2001 included only patients with 0, 1 or 2 grade lesions. Of the other 2 trials, Doctor 1992 included any diabetic patient with a chronic foot lesion whilst Abidia 2003 included patients with lesions present for more than 6 weeks where the ulcers were between 1 and 10 cm in diameter. Both these trials are likely to have included patients with a broad range of Wagner grades and in such cases, particularly where trials are small, imbalance across treatment arms for wound size or severity is highly likely at entry into the trial.

Venous ulcers.

Hammarlund 1994 included patients with ulceration for at least 1 year, and who did not display any 'tendency to heal' in the 2 months prior to enrolment.

BLINDING

Diabetic ulcers.

Two trials (Doctor 1992; Faglia 1996) appear to have been completely unblinded, while the remaining 2 trials describe patient blinding by sham therapy. Abidia 2003 also states that the treat-

ing physician and the outcome assessor were blinded although the hyperbaric facility chamber operator was aware of allocation. Abidia 2003 also assessed patient blinding as successful (majority of patients in both groups guessed they were receiving HBOT). We cannot exclude that in the 2 non-blinded trials, management decisions such as when to debride or amputate, were made in the knowledge of treatment allocation. This may constitute a potential for bias in these trials.

Venous ulcers.

Hammarlund 1994 states that patients, treating physician and outcome assessor were blinded.

PATIENTS LOST TO FOLLOW-UP

The numbers of patients lost to final follow-up are summarised in Table 1. There were no patients withdrawn or lost to follow-up who appeared in the analysis in any of the studies. Sensitivity analysis in this review has made best and worse case analyses to examine potentially important effects on outcome. Overall, there were 7 patients lost to final follow-up (4.3% of the total number enrolled).

INTENTION TO TREAT ANALYSIS

Only Abidia 2003 specified analysis by intention to treat. In the remaining 4 trials, while patients lost to follow-up or withdrawn were excluded from analysis, there was no re-allocation to placebo in patients who failed to complete active therapy. No information is available on these patients.

Effects of interventions

DIABETIC ULCERS (*Comparison 1)*

PRIMARY OUTCOMES

1. Proportion of ulcers healed at end of treatment period (6 weeks) (*Comparison 1, Outcome 01*)

Only 1 trial reported this outcome (Abidia 2003), involving 18 patients (12% of the total diabetic patients in this review), with 9 patients randomised to each treatment option. There was no statistically significant increase in the proportion of ulcers healed following HBOT (the RR of failing to heal with sham treatment was 2.33, 95%CI 0.92 to 5.93, P=0.07). A pre-planned sensitivity analysis examining the effect of allocation of dropouts suggested a borderline benefit with HBOT in the best case scenario but not the worst case scenario (best case risk of failing to heal with sham is 2.6, 95%CI 1.0 to 6.9, P=0.04, worst case RR 1.8, 95%CI 0.8 to 3.9, P=0.18) (*Comparison 1, Outcome 02 and 03*). The absolute risk difference between sham and HBOT in the best case scenario is significant (P=0.04), with an NNT to avoid 1 failure to heal of 2 (95% CI 1 to 11).

2. Proportion of ulcers healed at 6 months (*Comparison 1, Outcome 04*)

Only 1 trial reported this outcome (Abidia 2003), involving 18 patients (12% of the total diabetic patients in this review), with 9 patients randomised to each treatment option. There was no significant increase in the proportion of ulcers healed following HBOT (the RR of failing to heal with sham treatment was 1.8, 95%CI 0.8 to 3.9, P=0.32). A pre-planned sensitivity analysis examining the effect of allocation of dropouts did not alter this result. (Best case risk of failing to heal with sham is 2.3, 95%CI 0.9 to 6.3, P=0.09, worst case RR 1.5, 95%CI 0.6 to 3.6, P=0.36) (*Comparison 1, Outcome 05 and 06*).

3. Proportion of ulcers healed at 1 year (*Comparison 1, Outcome 07*)

Only 1 trial reported this outcome (Abidia 2003), involving 18 patients (12% of the total diabetic patients in this review), with 9 patients randomised to each treatment option. There was a significant increase in the proportion of ulcers healed following HBOT (the RR of failing to heal with sham treatment was 2.3, 95%CI 1.1 to 4.7, P=0.03). These efficacy data relate to a NNT to avoid 1 failure to heal of 2, 95%CI 1 to 5. However this result was sensitive to the allocation of dropouts. Best case risk of failing to heal with sham is 3.0, 95%CI 1.2 to 7.6, P=0.02, worst case RR 2.0, 95%CI 0.9 to 4.3, P=0.08) (*Comparison 1, Outcome 08 and 09*).

4. Proportion of patients requiring major amputation (*Comparison 1, Outcome 10*)

3 trials reported this outcome at final follow-up (Doctor 1992 (at discharge); Faglia 1996 (7 weeks); Abidia 2003 (1 year)), involving 118 patients (80% of the total diabetic patients in this review), 60 were randomised to HBOT, 58 to sham or control. Faglia contributed 59% of the patients in this analysis. There was a significant reduction in amputation rate with the application of HBOT (the RR of major amputation with HBOT was 0.31, 95%CI 0.13 to 0.71, P=0.006), and heterogeneity did not account for a significant proportion of the variability between studies (I^2 =0). This result was not sensitive to the allocation of dropouts (best case RR of amputation 0.28, 95%CI 0.12 to 0.64, P=0.002, worst case 0.41, 96%CI 0.19 to 0.86, P=0.02) (*Comparison 1, Outcome 11 and 12*).The NNT to avoid one amputation is 4, 95%CI 3 to 11. Neither was this result sensitive to the allocation of subjects to treatment arms in the Doctor trial (we considered extremes of 20 HBOT versus 10 control and 10 HBOT versus 20 control) (*Comparison 1, Outcome 18 and 19*). Subgroup analysis by number of treatments revealed a RR for amputation after 30 or more treatments of 0.32, 95%CI 0.11 to 0.91, P=0.03. For <30 treatments RR was 0.29, 95%CI 0.07 to 1.16, P=0.08. In the light of the fact that the magnitude of effect was similar between subgroups this result should be interpreted with caution. Subgroup analysis according to the use of sham therapy versus no use of sham suggests that the beneficial effect is lost with the employment of sham (RR of amputation with sham 1.0, 95%CI 0.7 to 13.6, P=1.0. RR without sham 0.27,95%CI 0.11 to 0.66, P=0.003) (*Comparison 1, Outcome 22*).

SECONDARY OUTCOMES

1. Proportion of patients requiring minor amputation

2 trials reported this outcome at final follow-up (Doctor 1992;

Abidia 2003), involving 48 patients (33% of the total diabetic patients in this review), 24 randomised to HBOT, 24 to sham or control. Doctor 1992 contributed 63% of the patients in this analysis. There was no significant change in rates of minor amputation with the application of HBOT (the RR of minor amputation with HBOT was 2.2, 95%CI 0.6 to 8.8, P=0.26) (*Comparison 1, Outcome 13*), and heterogeneity did not account for a significant proportion of the variability between studies (I^2 =0). This result was not sensitive to the allocation of dropouts (best case RR of amputation 1.7, 95%CI 0.5 to 6.2, P=0.45, worst case 2.6, 96%CI 0.7 to 10.0, P=0.16) (*Comparison 1, Outcome 14 and 15*). Neither was this result sensitive to the allocation of subjects in the Doctor trial, although with extreme allocation imbalance of 10 subjects to HBOT and 20 to control, the difference does approach significance, with the risk of suffering a minor amputation in the HBOT arm of 3.7 (95%CI 0.95 to 14.7), P=0.06 (*Comparison 1, Outcome 20 and 21*).

2. Transcutaneous oxygen tension change in affected foot after treatment

Only 1 trial contributed results to this outcome (Faglia 1996) involving 70 patients, 36 randomised to HBOT and 34 to control regimen. 2 patients dropped out at this analysis (1 control, 1 HBOT). There was a significantly greater increase in transcutaneous oxygen tension following HBOT (HBOT 14 mmHg, sham 5 mmHg, WMD 9 mmHg, 95%CI 4.7 mmHg to 13.3, P= 0.0001).

3. Absolute transcutaneous oxygen tensions in affected foot after treatment

3 trials contributed results to this outcome (Faglia 1996; Lin 2001; Abidia 2003), involving 117 patients, 62 randomised to HBOT, 55 to control. Faglia 1996 contributed 59% of the patients to this analysis, and 4 patients dropped out (2 control, 2 HBOT). Transcutaneous oxygen tensions in the affected foot were significantly higher in those patients who had received HBOT (HBOT 11.8 mmHg higher, 95%CI 5.7 mmHg to 17.8 mmHg, P=0.0002, Heterogeneity was low to moderate and accounted for about 1/4 of the variability between studies (I^2 = 25.4%).

There was no data available on time to complete healing, rate of wound size reduction, quality of life or recurrence rate.

VENOUS ULCERS (*Comparison 2)*

PRIMARY OUTCOMES

1. Proportion of ulcers healed at 18 weeks (*Comparison 2, Outcome 01*)

Only 1 trial contributed results to this outcome (Hammarlund 1994) involving 16 patients, 8 randomised to each treatment option. There was no significant increase in the proportion of ulcers healed in the HBOT group compared to a sham treatment (the RR of failing to heal with sham compared to HBOT is 1.33, 95%CI 0.89 to 1.99, P=0.16). A pre-planned sensitivity analysis examining the effect of allocation of dropouts using a best case (all dropouts in active group deemed successes, all dropouts in sham group deemed failures) and worse case (all dropouts in the active group deemed failures, all in the sham group deemed successes) did not alter the result (best case risk of failing to heal with sham is of borderline significance with a RR of 2.0, 95%CI 1.0 to 4.0, P=0.05, worst case RR 0.59, 95%CI 0.06 to 4.76, P=0.59) *(Comparison 1, Outcome 02 and 03).*

SECONDARY OUTCOMES

2. Reduction in wound area immediately after treatment (6 weeks) (*Comparison 1, Outcome 04*)

Only 1 trial contributed results to this outcome (Hammarlund 1994) involving 16 patients, 8 randomised to each treatment option. There was a significantly greater reduction wound area following HBOT. There was a reduction in wound area in the HBOT group of 35.7% compared to 2.7% in the sham group, (WMD 33%, 95%CI 19% to 47%, P<0.00001).

3. Reduction in wound area at 18 weeks, (*Comparison 1, Outcome 05*)

Only 1 trial contributed results to this outcome (Hammarlund 1994) involving 16 patients, 8 randomised to each treatment option. 5 patients dropped out at this analysis (3 sham, 2 HBOT). There was no significant difference in wound area reduction (HBOT 55.8%, sham 29.6%, WMD 29.6%, 95%CI -23.0% to 82.2%, P=0.27).

There was no data available on quality of life, pain reduction or recurrence rates for venous ulcers.

ARTERIAL AND PRESSURE ULCERS

No eligible trials were found 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. The other 3 trials simply did not report on adverse events or complications of therapy in either arm.

A table of NNT values at the expected event rates (those reported in control groups of these studies) is presented for those analyses where there was no significant differences in outcomes on meta-analysis above (Table 2). NNTs will change if the base rate expectation of a particular outcome in the population of interest varies from those in this review. In those cases, the NNTs here should be recalculated for the new base rate.

DISCUSSION

This review has included data from 5 trials, 4 of which concern diabetic foot ulcers. We believe these represent all randomised human trials in this area, both published and unpublished at the time of searching the databases. We found little evidence that HBOT speeds the healing of diabetic foot ulcers and limited evidence that it decreases major amputation. We found no evidence that HBOT increases the healing of venous ulcers, arterial or pressure ulcers. Only 5 trials with 163 patients in total were eligible for evaluation

using the large number of planned comparisons, and meta-analysis was not possible for many of these outcomes. Other problems for this review were the poor methodological quality of many of these trials (Jadad scores: 3 trials scored 2, 1 trial 4 and 1 trial 5), variability in entry criteria and the nature and timing of outcomes, and poor reporting of both outcomes and methodology. In particular, there is a possibility of bias due to differential wound size or severity on entry to these small trials, as well as from non-blinded management decisions in 3 trials (Abidia 2003, Faglia 1996, Lin 2001). A statistically significant benefit for HBOT was suggested in reducing the proportion of diabetic patients undergoing a major amputation and for the chance of having a healed lesion at 1 year from the start of therapy, while for patients with venous ulceration, their wounds were significantly smaller at 6 weeks, but not at 18 weeks. We were particularly surprised that only 1 trial (Abidia 2003) reported the proportion of diabetic ulcers that were healed at any time.

These trials were published over an 11 year period up to 2003, and from a wide geographical area. We had planned to perform subgroup analyses with respect to wound grade on admission, 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 subgroup analysis in diabetic ulcer trials by number of treatments in the course of HBOT and the use of sham therapy. Patient inclusion criteria were not standard and poorly reported in some trials. The diabetic foot ulcer trials either described lesions as chronic (Doctor 1992), present for >6 weeks (Abidia 2003), or of particular Wagner grades of severity (Lin 2001; Faglia 1996), but not both. The oxygen dose at each treatment was fairly consistent across trials, the lowest being 2.2 ATA for some patients in Faglia 1996, 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 4 treatments were administered over 4 weeks. While subgroup analysis by treatment number suggests the benefit of HBOT was lost with the short course (>30 treatment course risk of amputation with HBOT: RR 0.32, P=0.03, <30 treatment course: RR 0.29, P=0.08), the magnitude of effect was similar in the two subgroups and this result should be interpreted with great caution. While all trials used 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 an analysis of the use of sham versus no sham.

Pooled data for clinical outcomes of interest could only be performed for diabetic foot lesions and with respect to the risk of major and minor amputation. While HBOT did not affect the secondary outcome of minor amputation rate, the risk of major amputation was statistically significantly reduced with HBOT (RR 0.31, 95%CI 0.13 to 0.71, P=0.006). Although heterogeneity did not seem to be an issue with this analysis (I^2 =0%), it should be noted 2 of the 3 studies were small (8 and 15 subjects per arm), and 1 study (Faglia 1996) contributed more than half of the patients for this analysis (59%). This analysis suggests that we would need to treat 4 patients with HBOT in order to avoid 1 major amputation (NNT 4, 95%CI 3 to 11) and was not sensitive to the allocation of dropouts. Given the small number of subjects and generally poor quality of these trials, this result needs to be interpreted with caution. This is particularly so when considering that subgroup analysis by the use of sham therapy suggests the beneficial effect is lost in the small trial where a sham HBOT session was employed to blind the patient to treatment allocation. Furthermore, it is not clear if the surgical decision to amputate was made while blinded to treatment allocation, and this is an important potential source of bias and thus a threat to validity of these results. The 2 non-clinical outcomes of transcutaneous oxygen tension changes over the course of treatment and the absolute difference between HBOT and control groups both suggest significant improvement with the administration of HBOT and support the therapeutic mechanism proposed.

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 5 patients, and concluded that, while these studies suggested that HBOT might be of benefit in nonhealing diabetic ulcers, the overall study 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 study (Hammarlund 1994) which indicated a significant reduction in wound area at 6 weeks following the administration of HBOT (33% WMD 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 dropouts. 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.

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 and any effect on the quality of life for these patients, we have located no relevant data. One trial evaluated the economic impact of the application of HBOT (Abidia 2003), and this trial suggested a saving of £2,960.00 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 patients recover spontaneously over a period of days to weeks, a small proportion of patients 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 limited evidence that HBOT reduces the rate of major amputation in people who have chronic foot ulcers as a result of diabetes. Thus, the application of HBOT to these patients may be justified where HBOT facilities are available however an economic evaluation should be undertaken. Furthermore the small number of studies, the modest numbers of patients and the methodological and reporting inadequacies of the primary studies included in this review demand a cautious interpretation. To date no useful information regarding the efficacy or effectiveness of HBOT for chronic wounds with other underlying pathologies can be provided.

Implications for research

There is insufficient evidence to recommend the routine use of HBOT in the clinical treatment schedule for people with diabetes related foot ulcers. There is a strong case for further 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. Any future trials would need to consider in particular:

- Appropriate sample sizes with power to detect expected differences
- Careful definition and selection of target patients
- 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
- 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 (diabetic foot ulcers).

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* *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 diabetic patients with foot ulcers for >6/52, 1-10 cm diameter
Interventions	HBOT at 2.4 ATA for 90 minutes on 30 occasions over 6 weeks versus standard care consisting of a specialised multidisciplinary wound management program
Outcomes	Healed, major amputation, minor amputation, transcutaneous oxygen
Notes	Jadad score 5

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Doctor 1992

Methods	Randomised controlled trial. No blinding
Participants	30 diabetic patients referred with chronic foot lesion
Interventions	HBOT at 3.0 ATA on 4 occasions over 4 weeks versus standard care consisting of a specified surgical and dressing regimen
Outcomes	Major amputation, minor amputation
Notes	Jadad score 2 Unusual HBOT regimen

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Faglia 1996

Methods	Randomised controlled trial. No blinding
Participants	70 diabetic patients with foot lesion Wagner grade 2 to 4
Interventions	HBOT at 2.2 to 2.5 ATA for 90 minutes on an average of 39 occasions over about 6 weeks versus standard care consisting of a specialised multidisciplinary wound management program
Outcomes	Major amputation, transcutaneous oxygen
Notes	Jadad score 2

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Hammarlund 1994

Methods	Randomised, controlled trial. Allocation concealed by enrolment and randomisation as separate events. Participants and observers blinded
Participants	Venous ulceration >1yr with normal ABI. Air group wound area (mm2) 926 sd 752, HBOT wound area (mm2) 1058, sd 976
Interventions	HBOT at 2.5 ATA for 90 minutes on 30 occasions over 6 weeks versus air breathing sham treatment on the same schedule
Outcomes	Ulcer healing and reduction in area
Notes	Jadad score 4

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Lin 2001

Methods	Randomised controlled trial. Allocation made after decision to enrol, and patient blinded
Participants	29 diabetic patients with foot lesion Wagner grade 0-2
Interventions	HBOT at 2.5 ATA for 120 minutes daily to 30 treatments versus a comparator not specified (sham/no treatment)

Lin 2001 (*Continued*)

Outcomes	Transcutaneous oxygen
Notes	Jadad score 4 Abstract only

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

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

Study	Reason for exclusion
Abidia 2001c	No appropriate outcome data
Baroni 1987	Not randomised
Chin 2001	No appropriate outcome data
Faglia 1996a	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
Oriani 1990	Not randomised
Perrins 1967	Acute burn wound
Whelan 2001	Animal study
Zamboni 1997	Not randomised

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)	1	16	Risk Ratio (M-H, Fixed, 95% CI)	2.33 [0.92, 5.93]
2 Healed at end of treatment. Best case	1	18	Risk Ratio (M-H, Fixed, 95% CI)	2.67 [1.03, 6.91]
3 Healed at end of treatment. Worst case.	1	18	Risk Ratio (M-H, Fixed, 95% CI)	1.75 [0.78, 3.93]
4 Healed at 6 months	1	18	Risk Ratio (M-H, Fixed, 95% CI)	1.75 [0.78, 3.93]
5 Healed at 6 months. Best case.	1	18	Risk Ratio (M-H, Fixed, 95% CI)	2.33 [0.87, 6.27]
6 Healed at 6 months. Worst case.	1	18	Risk Ratio (M-H, Fixed, 95% CI)	1.5 [0.63, 3.56]
7 Healed at 1 year.	1	18	Risk Ratio (M-H, Fixed, 95% CI)	2.11 [1.05, 4.25]
8 Healed at 1 year. Best case.	1	18	Risk Ratio (M-H, Fixed, 95% CI)	2.71 [1.15, 6.39]
9 Healed at 1 year. Worst case.	1	18	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.93, 4.30]
10 Major amputations	3	118	Risk Ratio (M-H, Fixed, 95% CI)	0.31 [0.13, 0.71]
10.1 subgroup (30+ treatments)	2	88	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.11, 0.91]
10.2 Subgroup (<30 treatments)	1	30	Risk Ratio (M-H, Fixed, 95% CI)	0.29 [0.07, 1.16]
11 Major amputations. Best case.	3	118	Risk Ratio (M-H, Fixed, 95% CI)	0.28 [0.12, 0.64]
12 Major amputations. Worst case.	3	118	Risk Ratio (M-H, Fixed, 95% CI)	0.41 [0.19, 0.86]
13 Minor amputations.	2	48	Risk Ratio (M-H, Fixed, 95% CI)	2.2 [0.56, 8.72]
14 Minor amputations. Best case.	2	48	Risk Ratio (M-H, Fixed, 95% CI)	1.67 [0.45, 6.18]
15 Minor amputations. Worst case.	2	48	Risk Ratio (M-H, Fixed, 95% CI)	2.6 [0.68, 10.01]
16 Transcutaneous oxygen tensions change after treatment	1	68	Mean Difference (IV, Fixed, 95% CI)	9.0 [4.68, 13.32]
17 Absolute difference in transcutaneous oxygen at end of treatment	3	113	Mean Difference (IV, Fixed, 95% CI)	11.76 [5.68, 17.84]
18 Major amputation sensitivity to Doctor trial. Allocation 20HBOT/10control	3	118	Risk Ratio (M-H, Fixed, 95% CI)	0.24 [0.11, 0.55]
19 Major amputation sensitivity to Doctor trial. Allocation 10 HBOT/20 Control	3	118	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.17, 0.89]
20 Minor amputation sensitivity to Doctor trial. Allocation 20HBOT/10control	2	40	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.24, 3.43]
21 Minor amputation sensitivity to Doctor trial. Allocation 10HBOT/20control	2	48	Risk Ratio (M-H, Fixed, 95% CI)	3.73 [0.95, 14.66]
22 Major amputation subgroup by use of sham	3	118	Risk Ratio (M-H, Fixed, 95% CI)	0.31 [0.13, 0.71]