Systematic review of hyperbaric oxygen in the management of chronic wounds

I. Roeckl-Wiedmann, M. Bennett and P. Kranke

Department of Anaesthesiology and Intensive Care Medicine, Rotkreuz-Krankenhaus, Munich, Germany, Department of Diving and Hyperbaric Medicine, Prince of Wales Hospital, University of NSW, Australia and Department of Anaesthesiology, University of Wuerzburg, Germany

Correspondence to: Dr P. Kranke, Department of Anaesthesiology, University of Wuerzburg, Oberduerrbacherstrasse 6, 97080 Wuerzburg, Germany (e-mail: kranke.p@klinik.uni-wuerzburg.de)

Background: Many therapeutic options exist for chronic wounds. Hyperbaric oxygen therapy (HBOT) is one such option. It may be used for diabetic, venous, arterial and pressure ulcers.

Methods: Following a systematic search of the literature, pooled analyses of predetermined clinical outcomes of randomized controlled trials involving the use of HBOT for chronic wounds were performed. Relative risks (RR) and number needed to treat (NNT) with 95 per cent confidence intervals (c.i.) were calculated.

Results: Six studies met the inclusion criteria. No appropriate trials were located for arterial and pressure ulcers. Pooled data from five trials on diabetic ulcers (118 patients) suggested a significant reduction in the risk of major amputation with HBOT (RR: 0.31; c.i. 0.13 to 0.71) with a NNT of 4 (c.i. 3 to 11). Sensitivity analyses did not alter the results. Ulcer healing and the rate of minor amputation were not influenced by HBOT. Data from one trial on venous ulcers suggested significant wound size reduction at the end of the treatment, but not at follow-up.

Conclusions: There is evidence that HBOT reduces the risk of major amputation in diabetic patients. For venous, arterial or pressure ulcers there is a lack of data. Further trials may be warranted.

Introduction

Chronic wounds are defined as lesions that take a long time to heal, fail to heal or recur.1,2. They are very common in industrialized countries and cause significant pain and discomfort.1 The true incidence and economic impact of chronic wounds are difficult to assess because of the wide range of causative diseases and available treatment options. Nevertheless, it has been suggested that 1 per cent of the population of western countries will suffer some kind of leg ulcer at some time, and the annual cost for the treatment of all chronic wounds may be as high as £1 billion in the UK alone. Chronic wounds are more common in elderly patients and in those with multiple health problems. With an aging population one may expect both the incidence and cost of chronic wounds to continue to rise.

Chronic wound types

The aetiology of chronic wounds is diverse. For this systematic review, four chronic wound types were considered. Diabetic foot ulcers are the most common chronic wounds in western industrialized countries. The prevalence of diabetes mellitus in the UK has been estimated at 2 per cent of the population, of whom 15 per cent will suffer foot ulceration. In these patients the amputation rate is 15–70 times higher than in the general population.9,10. Venous leg ulcers are caused by the presence of sustained high venous pressures secondary to reflux or obstruction.11. The prevalence of venous leg ulcers ranges between 1-5 and 3 per 1000 adults and increases up to 20 per 1000 for those over 80 years.12. Arterial leg ulcers are caused by arterial insufficiency and usually indicate general arteriosclerosis.13. 25 per cent of leg ulcers are likely to be arterial.14. Pressure ulcers are caused by unrelieved pressure or friction. Increased age, immobility and malnutrition are risk factors.15. The prevalence of pressure ulcers in NHS hospitals in the UK is about 10 per cent.16.
Treatment options and wound healing

Wound management varies according to aetiology and includes treatment of the underlying pathology (e.g. bypass surgery for arterial ulcers), systematic treatment (e.g. nutritional supplements), and local treatment designed to improve the wound environment (e.g. dressings and pressure-relieving mattresses). There are many other treatment options but, despite multiple simultaneous and sequential therapeutic approaches, chronic wounds are highly resistant to treatment and are often indolent or even slowly progressive.

Wound healing is multifaceted. Some stages of the process appear to be triggered by hypoxia (e.g. angiogenesis)\textsuperscript{17,18}, while other phases of tissue repair are oxygen-dependent (e.g. fibroblast proliferation and bacterial killing by macrophages)\textsuperscript{19–21}. A delicate balance between intra-wound hypoxia as a consequence of blood vessel disruption and peri-wound oxygenation seems to be associated with successful healing. Wounds that occur in hypoxic tissue beds, however, are often resistant to healing\textsuperscript{22,23}. Improving oxygenation in the microenvironment surrounding the wound might enhance healing\textsuperscript{19,22,24}.

Hyperbaric oxygen treatment

Hyperbaric oxygen therapy (HBOT) has been proposed as a useful adjunct in the treatment of problematic wounds\textsuperscript{25}. HBOT is defined as the administration of oxygen at pressures greater than 1 atmosphere absolute (ATA) and has been shown \textit{in vivo} to cause hyper-oxygenation of normal tissue and of tissue with poor blood perfusion\textsuperscript{26}. Arterial oxygen tensions of greater than 1000 mmHg are routinely achieved during HBOT and such tensions in plasma cause up-regulation of growth factors, down-regulation of inflammatory cytokines\textsuperscript{23,26,27}, increased fibroblast activation, angiogenesis, antibacterial effects and enhanced antibiotic action\textsuperscript{28–30}.

HBOT is always presented as an adjunctive therapy to normal wound care measures\textsuperscript{31}. Its administration requires the patient to be confined within an airtight vessel and given 100 per cent oxygen for respiration. HBOT sessions are usually conducted from 45 to 120 minutes once or twice daily at pressures between 1·5 and 3·0 ATA. A typical course of treatment for a chronic wound involves 20 to 30 such sessions\textsuperscript{31}.

Oxygen in high doses is toxic, particularly in richly perfused tissue such as the brain (acute cerebral oxygen toxicity) and lungs (chronic pulmonary oxygen toxicity). Acute cerebral toxicity occurs in approximately 1 in 2000 exposures and does not result in any permanent injury, while the pulmonary changes are dose-related and reversible at doses used therapeutically\textsuperscript{32}. Other potential risks associated with HBOT include damage to the ears, sinuses and lungs from the effect of pressure (barotrauma) and the psychological effect of confinement\textsuperscript{25,31}.

Despite promising experimental findings both \textit{in vitro} and in a number of animal models, the clinical evidence of the effectiveness of HBOT in healing chronic wounds is sparse and difficult to interpret\textsuperscript{13,14}. The object of this systematic review was to assess the randomized controlled trial (RCT) evidence of impact of HBOT in the management of diabetic, venous, arterial and pressure ulcers.

Patients and methods

Inclusion and exclusion criteria

RCTs were eligible for inclusion if they compared the effect of adjunctive HBOT with no HBOT or sham therapy on air for chronic wound healing. Only studies in which allocation to treatment was random were included; studies that enrolled patients with chronic wounds associated with diabetes mellitus, venous or arterial disease, or external pressure were accepted. Chronic wounds were defined as wounds that had failed to heal with specific wound therapies and had not received HBOT previously. Animal studies and studies dealing with topical HBOT were excluded.

Outcome measurements

All clinically important possible outcomes were predetermined. Studies were eligible for inclusion if they reported at least one of the following outcome measures: wound size reduction, proportion healed, risk of major amputation (amputation of the lower or upper limb proximal the ankle or wrist) and minor amputation (amputation of the distal end of hand or foot), pain, recurrence rate after healing, quality of life or transcutaneous oxygen tension (\textit{TcPO}$_2$) changes. Any reported adverse events of HBOT were also recorded.

Search strategy

Specific search strategies were developed to identify eligible reports from Medline (1966–2003), Embase (1974–2003), Cochrane Central Register of Controlled Trials (CENTRAL) (1988–2003) and DORCTHIM (1998–2003). This last is a specifically designed database of RCTs in hyperbaric medicine (http://www.hboevidence.com). The results of these searches were cross-referenced with the Cochrane Wounds Group Special Trials Register, which
contains citations of trials from 19 electronic databases. Medical subject headings (MeSH) and main key words used were ‘wounds and injuries’, ‘ulcer’, ‘skin ulcer’, ‘foot ulcer’, ‘leg ulcer’, ‘varicose ulcer’, ‘venous ulcer’, ‘diabetic foot’, and ‘hyperbaric oxygenation’. Variants of the main key words and free text terms were applied. No restrictions of language were made. Relevant hyperbaric textbooks, journals and conference proceedings were hand searched. Experts in the field were contacted for published, unpublished and ongoing RCTs. Additional trials were identified from the citations within obtained papers.

Data extraction and management
The reviewers independently assessed the electronic search results and selected potentially relevant studies. Disagreements were settled by examination of the full paper and consensus. The quality scale of Jadad35 was applied to assess methodological quality and detect potential sources of bias; this scale assesses randomization, blinding and description of withdrawals. We further recorded the adequacy of allocation concealment. Relevant data on study design, disease aetiology, included patients, intervention and reported outcome measurements were recorded on an extraction form designed for this review. If any relevant data were missing from trial reports, the authors were contacted. To allow an intention to treat analysis, the data reflecting the original allocation group were extracted. Losses to follow-up were reported. Disagreements were again settled by consensus. Following agreement, the data were entered into Review Manager® 4.2-1. (Cochrane Collaboration, Oxford, UK) for analysis.

Statistical analyses
Trials were grouped by wound aetiology. For dichotomous outcomes (e.g. risk of amputation) relative risks (RR) with 95 per cent confidence interval (c.i.) was calculated. A statistically significant difference from control was assumed when the 95 per cent c.i. of the RR did not include the value 1-0. For continuous outcomes (e.g. percentage wound size reduction), the weighted mean difference (WMD) between groups with 95 per cent c.i. was calculated. A fixed-effects model was used when heterogeneity between the studies was not likely and a random-effects model when heterogeneity was likely. Heterogeneity was assessed using the $I^2$ statistic, which describes the variability in effect estimate across studies that is due to differences between studies rather than random sampling error. Heterogeneity was deemed significant if the $I^2$ analysis suggested more than 30 per cent of the variability in an analysis was due to differences between trials. Consideration was then given to the appropriateness of pooling and meta-analysis. Number needed to treat (NNT) and number needed to harm (NNH) with 95 per cent c.i. were calculated when the RR estimates were statistically significant. Sensitivity analyses were carried out for missing data using best-case and worst-case scenarios. The best-case scenario assumed that none of the originally enrolled patients missing from the primary analysis in the HBOT group had the negative outcome of interest while all those missing from the control group did. The worst-case scenario was the reverse.

Results
Excluded and included studies
The initial search yielded 78 articles, of which 21 were considered to be suitable human trials dealing with the treatment of chronic wounds using adjunctive systematic HBOT16–56. Appraisal of the full report of these papers led to the exclusion of 15 publications because of non-random allocation37–39,40,45,47,54, use of topical HBOT38,46, chronic wound aetiology other than defined16, not entirely limited to humans53, no appropriate outcome data44,51 or repeat publication of the same dataset48–50.

Six publications met the inclusion criteria41–43,52,55,56. Five included patients with diabetic foot ulcers41,43,52,55,56 and one included patients with venous ulcers52. No eligible trials were found investigating the impact of HBOT on arterial or pressure ulcers. The total number of patients was 191,100 receiving a standard wound protocol plus HBOT, and 91 standard wound protocol alone (control).

Clinical characteristics
A total of 175 patients with diabetic ulcers were included, 92 receiving HBOT and 83 controls. Inclusion criteria varied between the trials. Doctor et al.41 included any diabetic with a chronic foot lesion, Lin et al.52 and Faglia et al.43 patients with ulcers of Wagner grade 0 to 2 and 2 to 4 respectively, while Abidia et al.56 specified diabetic foot ulcers with a size of 1–10 mm diameter for at least 6 weeks. Treatment pressure (2-2 to 3-0 ATA), time schedule (45 to 120 min), and number of sessions (30 to 38) of HBOT differed between trials. Lin et al.52 and Abidia et al.56 used a blinded sham regimen, while the remaining trials did not41,43,55. All described a multidisciplinary wound management strategy covering items like optimization of metabolic control, antibiotics, wound care, podiatry, orthopaedic shoe, and vascular surgery in both groups. The follow-up period ranged from immediately following
the last HBOT session\(^2\) to 1 year\(^5\). Individual trial characteristics are given in Table 1.

Only one study\(^4\) was found dealing with venous ulcers. The duration of persistent ulcers was at least 1 year before enrolment. Sixteen patients were randomized, eight receiving usual wound care plus HBOT and eight receiving usual wound care plus sham therapy. HBOT was 2.4 ATA for 90 minutes to a total of 30 sessions over 6 weeks. Patients with chronic illnesses such as diabetes and smokers were excluded (Table 1).

Methodological characteristics

Abidia et al.\(^5\) scored all 5 points on the Jadad scale. Randomization was reliably concealed. They employed a sham therapy with air and blinded all participants except the hyperbaric facility operator. The blinding in their study was deemed successful because the majority of patients in both groups guessed they were receiving HBOT. Lin et al.\(^5\) scored 4 points after supplying further information concerning randomization concealment and sham therapy. The other studies\(^\) scored 2 points each because they did not adequately describe randomization procedures, appeared to have been completely unblinded and did not use sham therapy.

Hammarlund and Sundberg\(^4\) scored 4 points and appeared to conceal allocation adequately. The authors employed sham therapy.

Outcomes

Statistical pooling was not possible for the majority of preplanned outcome measures owing to lack of suitable data. Problems included the small number of studies, the modest number of patients and the variability in outcome measures employed. The individual data are presented in Table 2.

Diabetic ulcer

Proportion healed

Two trials reported the proportion of ulcers healed in the period immediately after\(^6\) and 2 weeks after\(^5\) HBOT. These two studies involved 46 patients (26 per cent of the diabetic patients in this review), 24 receiving HBOT and 22 controls. Seven ulcers (29 per cent) healed in the HBOT group versus one (5 per cent) in the control group,

Table 1 Characteristics of included studies

<table>
<thead>
<tr>
<th>Reference and year</th>
<th>Description of chronic wounds</th>
<th>No. of patients</th>
<th>Control treatment</th>
<th>Intervention treatment</th>
<th>Outcomes</th>
<th>Jadad score*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic ulcers</td>
<td></td>
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<tr>
<td>Doctor et al., 1992(^1)</td>
<td>Not specified</td>
<td>30</td>
<td>Multi-disciplinary wound care only</td>
<td>Multi-disciplinary wound care plus HBOT 4 times, 45 min, 3.0 ATA</td>
<td>Major amputation, minor amputation</td>
<td>2</td>
</tr>
<tr>
<td>Faglia et al., 1996(^4)</td>
<td>&gt; 3 months, Wagner grade 2–4, signs of neuropathy similar in both groups</td>
<td>70</td>
<td>Multi-disciplinary wound care only</td>
<td>Multi-disciplinary wound care plus HBOT 30 times, 90 min, 2.2–2.5 ATA</td>
<td>Major amputation, TcPO(_2)</td>
<td>2</td>
</tr>
<tr>
<td>Lin et al., 2001(^2)</td>
<td>Duration not specified, Wagner grade 0–2</td>
<td>29</td>
<td>Control treatment not specified plus sham therapy on air</td>
<td>Control treatment not specified plus HBOT 30 times, 120 min, 2.5 ATA</td>
<td>TcPO(_2)</td>
<td>4</td>
</tr>
<tr>
<td>Kessler et al., 2003(^5)</td>
<td>&gt; 3 months, Wagner grade 1–3, signs of neuropathy in all patients</td>
<td>28</td>
<td>Multi-disciplinary wound management only</td>
<td>Multi-disciplinary wound management plus HBOT 20 times, 90 min, 2.5 ATA</td>
<td>Proportion of ulcers healed, wound size reduction</td>
<td>2</td>
</tr>
<tr>
<td>Abidia et al., 2003(^5)</td>
<td>Diabetes mellitus, ischaemic, &gt; 6 weeks, 1–10 mm diameter</td>
<td>18</td>
<td>Multi-disciplinary wound clinic plus sham therapy on air</td>
<td>Multi-disciplinary wound clinic plus HBOT 30 times, 90 min, 2.4 ATA</td>
<td>Proportion of ulcers healed, minor/major amputation, TcPO(_2)</td>
<td>5</td>
</tr>
<tr>
<td>Venous ulcer</td>
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<tr>
<td>Hammarlund and Sundberg, 1994(^2)</td>
<td>&gt; 1 year duration, normal ABI</td>
<td>16</td>
<td>Usual care plus sham therapy on air</td>
<td>Usual care plus HBOT 30 times, 90 min, 2.5 ATA</td>
<td>Proportion of ulcers healed, wound size reduction</td>
<td>4</td>
</tr>
</tbody>
</table>

but pooled data from these two studies suggested that there was no significant difference in the proportion of ulcers healed between the groups (RR: 0.99 per cent c.i. 0.94 to 2.42) within 2 weeks of HBOT. Heterogeneity did not account for a significant proportion of the variability between studies ($I^2 = 0$ per cent). The effect of allocation of dropouts suggested a benefit with HBOT in the best-case scenario (RR: 6.04; 95 per cent c.i. 1.23 to 29.80), but not in the worst-case scenario (RR: 2.89; 95 per cent c.i. 0.83 to 10.14).

Only one trial \textsuperscript{56} reported the proportion of ulcers healed at final follow-up at 1 year. This study involved 18 patients, nine in each group, and covered 10 per cent of the diabetic patients in this review. Five ulcers (56 per cent) healed in the HBOT group versus one (11 per cent) in the control group. The study suggests a significantly higher proportion of ulcers were healed in patients following a course of HBOT (RR: 2.25; 95 per cent c.i. 1.08 to 4.67) compared with patients with standard wound protocol after 1 year. This result was, however, sensitive to the allocation of dropouts (best-case scenario: RR: 3.00; 95 per cent c.i. 1.19 to 7.56), with significance lost in a worst-case scenario (RR: 2.00; 95 per cent c.i. 0.93 to 4.30).

### Wound size reduction

One trial \textsuperscript{55} reported wound size reduction. This study involved 28 patients, 15 patients receiving HBOT and 13 controls, and covered 16 per cent of the diabetic patients in this review. There was a significant wound size reduction of approximately 20 per cent immediately following a course of HBOT (WMD: 20.10, 95 per cent c.i. 4.26 to 35.94), but not at final follow-up 4 weeks later (WMD: 6.8, 95 per cent c.i. –9.80 to 23.40).

### Major amputation

Three trials \textsuperscript{41,43,56} presented the rate of major amputation and involved 118 patients (67 per cent of the diabetic patients in this review). Doctor \textit{et al.} \textsuperscript{41} examined the major amputation rate at discharge, Faglia \textit{et al.} \textsuperscript{43} after 7 weeks and Abidia \textit{et al.} \textsuperscript{56} after 1 year. Faglia \textit{et al.} \textsuperscript{43}

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**Table 2: Outcomes assessed**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Studies</th>
<th>No. of patients</th>
<th>Efficacy data* and NNT with 95% c.i.</th>
<th>Best-case scenario</th>
<th>Worst-case scenario</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic ulcers</td>
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<tr>
<td>Wound size reduction at end of treatment (2 weeks)</td>
<td>Kessler \textit{et al.}\textsuperscript{55}</td>
<td>28</td>
<td>WMD: 20.10† (4.26, 35.94)</td>
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</tr>
<tr>
<td>Wound size reduction at 4 weeks</td>
<td>Kessler \textit{et al.}\textsuperscript{55}</td>
<td>28</td>
<td>WMD: 6.8</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Proportion healed within 2 weeks of treatment</td>
<td>Kessler \textit{et al.}\textsuperscript{55}</td>
<td>46</td>
<td>RR: 4.78 (0.94, 24.24)</td>
<td>RR: 6.04 (1.23, 29.80)</td>
<td>RR: 2.89 (0.83, 10.14)</td>
</tr>
<tr>
<td>Proportion healed at 6 months</td>
<td>Abidia \textit{et al.}\textsuperscript{56}</td>
<td>18</td>
<td>RR: 1.75</td>
<td>RR: 2.33 (0.87, 6.27)</td>
<td>RR: 1.50 (0.63, 3.56)</td>
</tr>
<tr>
<td>Proportion healed at final follow-up (1 year)</td>
<td>Abidia \textit{et al.}\textsuperscript{56}</td>
<td>18</td>
<td>RR: 2.25† (1.08, 4.67)</td>
<td>RR: 3.00† (1.19, 7.56)</td>
<td>RR: 2.00 (0.93, 4.30)</td>
</tr>
<tr>
<td>Difference in absolute transcutaneous oxygen tension before and after a HBOT course</td>
<td>Faglia \textit{et al.}\textsuperscript{43}</td>
<td>117</td>
<td>WMD (mmHg): 11.76† (1 to 5)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Major amputation at discharge\textsuperscript{41}, after 7 weeks\textsuperscript{43} and after 1 year\textsuperscript{56}</td>
<td>Lin \textit{et al.}\textsuperscript{52}</td>
<td>118</td>
<td>RR: 0.31† (0.13, 0.71)</td>
<td>RR: 0.28† (0.12, 0.64)</td>
<td>RR: 0.41† (0.19, 0.86)</td>
</tr>
<tr>
<td>Minor amputation at discharge\textsuperscript{41} and after 1 year\textsuperscript{56}</td>
<td>Doctor \textit{et al.}\textsuperscript{41}</td>
<td>48</td>
<td>RR: 2.20 (0.56, 8.72)</td>
<td>RR: 1.67 (0.45, 6.18)</td>
<td>RR: 2.60 (0.68, 10.01)</td>
</tr>
<tr>
<td>Venous ulcers</td>
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<tr>
<td>Proportion healed at 18 weeks</td>
<td>Hammarlund and Sundberg\textsuperscript{42}</td>
<td>16</td>
<td>RR: 1.33 (0.89, 1.99)</td>
<td>RR: 2.00 (1.00, 4.00)</td>
<td>RR: 0.83 (0.43, 1.63)</td>
</tr>
<tr>
<td>Wound size reduction at end of treatment (6 weeks)</td>
<td>Hammarlund and Sundberg\textsuperscript{42}</td>
<td>16</td>
<td>WMD: 33.00† (18.97, 47.03)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Wound size reduction at 18 weeks</td>
<td>Hammarlund and Sundberg\textsuperscript{42}</td>
<td>16</td>
<td>WMD: 29.60 (–22.99, 82.19)</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

*Using fixed effects model: WMD, weighted mean difference (%); RR, relative risks. †Significant outcomes (statistical difference is assumed if the 95 per cent c.i. does not include the value 1.0). NNT, number needed to treat; HBOT, hyperbaric oxygen therapy.
contributed 59 per cent of the patients. No heterogeneity was found between the studies ($I^2 = 0$). Sixty patients were randomized to HBOT and 58 to control. Six (10 per cent) underwent major amputation in the HBOT group versus 19 (33 per cent) in the control group. The risk of major amputation was significantly reduced with HBOT (RR: 0.31; 95 per cent c.i. 0.13 to 0.71). Sensitivity analyses did not affect the result. The NNT to avoid one major amputation was four (95 per cent c.i. 3 to 11).

Minor amputation
Two trials$^{41,56}$ reported the rate of minor amputation, and involved 48 patients (27 per cent of the diabetic patients in this review). Twenty-four patients were randomized to receive HBOT and 24 as controls. Doctor et al.$^{41}$ contributed 63 per cent of the patients. No heterogeneity was found between the studies ($I^2 = 0$). Five patients (21 per cent) underwent minor amputation in the HBOT group versus two (8 per cent) in the control group. Pooled data of these two trials suggested that the risk of minor amputation was increased with HBOT, but not significantly (RR: 2.20; 95 per cent c.i. 0.56 to 8.72). Sensitivity analyses for withdrawals did not alter the result.

Absolute difference in transcutaneous oxygen tensions
Three trials$^{43,52,56}$ reported absolute difference in transcutaneous oxygen tensions (TcPO$_2$) in the affected foot before and immediately after the treatment course. The trials involved 117 patients (67 per cent of the diabetic patients in this review) and the study of Faglia et al.$^{43}$ contributed 40 per cent of the patients. TcPO$_2$ was significantly higher in the HBOT group at the end of treatment (WMD: 11.76 mmHg, 95 per cent c.i. 5.67 to 17.84). Heterogeneity between studies was low to moderate ($I^2 = 25.4$ per cent).

Venous ulcer
Wound size reduction and proportion healed
Hammarlund and Sundberg$^{42}$ recruited 16 patients, randomized eight to treatment (usual wound care plus HBOT) and eight to control (usual wound care plus sham therapy). Mean wound area reduction immediately after treatment was significantly greater after HBOT (WMD: 33 per cent, 95 per cent c.i. 18.97 to 47.03). This effect persisted at 18 weeks’ follow-up, but was no longer statistically significant (WMD: 29.60 per cent, 95 per cent c.i. −22.99 to 82.19). However, five patients (two in the HBOT group and three in the control group) were not reported at final follow-up. There was no statistically significant difference in the chance of healing following HBOT (RR: 1.33; 95 per cent c.i. 0.89 to 1.99).

Adverse events of HBOT
Doctor et al.$^{41}$ and Abidia et al.$^{56}$ explicitly reported that there were no adverse events related to HBOT. Faglia et al.$^{43}$ and Kessler et al.$^{55}$ reported two instances of aural barotrauma, one of which caused withdrawal from treatment, while the other did not interrupt therapy. The other studies$^{52,56}$ did not report on adverse events or complications of therapy in either arm.

Discussion
HBOT has been suggested as a treatment option for chronic wounds for at least 40 years$^{57}$ and the rationale is well described in the literature$^{17,19,23,24,26–30,58,59}$.

Although HBOT is used throughout the world for patients with chronic wounds$^{25,31}$, it has not been widely adopted outside a small number of specialist centres, and there are few clinical data regarding effectiveness. Routine application remains controversial$^{33,34}$.

This systematic review provides some evidence that, for patients with diabetic ulcers resistant to standard care, HBOT decreases the risk of major amputation. Patients receiving HBOT are one-third as likely to require such an amputation as controls (RR: 0.31; 95 per cent c.i. 0.13 to 0.71) and it can be estimated that one need treat only four patients with HBOT to avoid one major amputation (95 per cent c.i. 3 to 11). The finding that TcPO$_2$ around the ulcers is significantly raised following a course of HBOT supports a mechanism for this benefit. On the other hand, this review is unable to confirm any significant benefit from HBOT on ulcer healing, wound area reduction or need for a minor amputation in patients with diabetic ulcers. There is a trend toward greater ulcer healing after HBOT but statistical significance cannot be realized on the small numbers of patients included in this analysis. For patients with venous ulceration, the one small randomized trial available suggests a benefit from HBOT with regard to ulcer area, but not healing. The authors were unable to find appropriate data to confirm or refute the long-term effect of therapy. No appropriate data were available on the effect of HBOT on healing of arterial or pressure ulcers.

Several problems exist. Only six randomized trials$^{41–43,52,55,56}$ were suitable for inclusion in this review. Study quality was very variable with most trials reporting methodology poorly. Blinding of the patients, investigators and/or outcome assessors was achieved in only two$^{52,56}$ trials. This is a potential source of bias$^{60–62}$, as was the often inadequate accounting of withdrawals$^{41,43,55,63}$. Small sample size (four trials had 30 patients or fewer) and different inclusion criteria between trials are further problems. Entry criteria ranged from ‘any chronic foot...
lesion\textsuperscript{41} or ‘chronic foot lesions for longer than six weeks’\textsuperscript{56} to ulcers with different Wagner grade classification\textsuperscript{41,52}, but not both. The authors are unable to state which ulcer grade is most likely to benefit from HBOT.

While the oxygen dose under study was relatively uniform across the trials, there was considerable variability in outcome measurements employed, making data pooling problematic. Surprisingly, only two studies\textsuperscript{55,56} recorded the proportion of ulcers healed at any time, and only one\textsuperscript{56} of these after an appropriate follow-up period.

The authors believe that all relevant studies were identified for this review. While publication bias is possible, they have consulted widely in the field and are not aware of any other completed but unreported studies.

For venous ulcers only the data from Hammarlund and Sundberg\textsuperscript{52} is available. This trial suggests that HBOT reduces ulcer area in the short term, but there is no evidence that the ulcers are more likely to heal. Apart from issues of power, the methodological quality of this study was reasonable but the high withdrawal rate (31 per cent) by the time of final follow-up at 18 weeks reduces confidence in the reported findings.

The included trials reported no major adverse effects in either treatment arm. Major adverse effects of HBOT are rare, and it is not surprising that none were reported in this small sample. However, from larger descriptive studies it is known that about 20 per cent of patients experience some degree of middle ear barotrauma, and 60 to 70 per cent a measurable, reversible worsening of myopia\textsuperscript{64}.

Present findings are comparable to those of previous reviews by Wunderlich\textsuperscript{33} and Wang\textsuperscript{34}. Both included studies with different designs and did not focus on RCTs. They concluded that HBOT may be beneficial as an adjunctive therapy for chronic non-healing diabetic wounds, compromised skin grafts, gas gangrene and irradiation injury\textsuperscript{33,34}.

In contrast to the work of those authors, however, the present review is of the randomized evidence alone, using Cochrane Collaboration methodology, to limit interest to trials of relatively high internal validity. Some evidence supports the use of adjuvant HBOT to treat chronic diabetic foot ulcers in order to avoid major amputation and possibly to improve the chance of healing, but the small numbers of patients and methodological problems necessitate a cautious interpretation of the results.

There is a need to verify any possible benefit of HBOT in a large RCT using healing as an outcome measure at clinically meaningful follow-up intervals. Such a trial should be appropriately powered, based on this review, and should include explicit entry criteria, allocation concealment and appropriate comparator therapy. While acknowledging the difficulties of employing sham therapy in this area, effective blinding strategies are possible and should be used. Economic evaluation of HBOT should also be studied. In the meantime, HBOT may be regarded as promising treatment option when other strategies have failed.

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