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Diabetic foot ulcers treated with hyperbaric oxygen therapy: a review of the literature

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Abstract

Hyperbaric oxygen therapy (HBO) has been used as an adjunct for healing diabetic foot ulcers (DFUs) for decades. However, its use remains controversial. A literature search was conducted to locate clinical studies and assess the available evidence. Ten prospective and seven retrospective studies evaluating HBO for DFUs were located. These were reviewed and the outcomes were discussed. One study reported no difference in outcomes between patients receiving hyperbaric oxygen and the control group. However, their regime differed from all other studies in that the patients received hyperbaric oxygen twice rather than once daily. Reduced amputation rates and improved healing were the most common outcomes observed.

Introduction

Central to the treatment of any diabetic foot ulcer (DFU) is good wound care, including debridement of devitalised tissue, offloading, optimising diabetic control and nutritional intake, use of antibiotics to treat infection and multidisciplinary input (1–3). Complications of DFUs, such as infections and gangrene, frequently lead to hospitalisation and amputation (4,5) and incur a significant cost economically, socially and psychologically. Much progress has been made in understanding the pathogenesis and management of the diabetic foot over the last 25 years (6). However, it is still suggested that a person with diabetes has a 15% risk of developing an ulcer and that 85% of non-traumatic amputations in diabetics are preceded by a foot ulcer (7). A study in Scotland observed that 68% of diabetic patients who had an amputation died within 5 years (8).

Hyperbaric oxygen therapy (HBO) has been recommended as a useful adjunct for DFUs failing to respond to wound treatment alone(9–12). HBO has been defined as the inhalation of 100% oxygen at pressures greater than sea level(13). Because of its relatively high costs, accessibility in some areas, reputed lack of evidence, and partly because of a history of unsubstantiated claims of its effectiveness in treating a variety of ailments(1,14), its use remains controversial.

The increased pressure and inspiration of high levels of oxygen during HBO have been shown not only to fully oxygenate the haemoglobin in the circulating blood, but also results in more oxygen being dissolved into the plasma, in proportion to the increased partial pressure(10,15). Boerema *et al*. (16) observed that during HBO, sufficient oxygen could be dissolved in the plasma to supply tissue oxygen requirements for basal metabolism without the support of haemoglobin. Oxygen dissolved in the plasma is more readily used than that bound to the haemoglobin and so under hyperbaric conditions oxyhaemoglobin will pass unchanged from the arterial to the venous circulation(17). This mechanism of oxygen transport has potential benefits for patients with DFUs who have ischaemia and peripheral vascular disease (PVD).

HBO is believed to stimulate angiogenesis, increase cell proliferation, minimise necrosis and facilitate infection prevention and treatment by elevating tissue oxygen tension(18). Vasoconstriction is another reported effect of HBO(15) which reduces oedema(19). Verklin and Mandell (20) observed that

Key Messages

- complications of diabetic foot ulcers incur a significant cost
- hyperbaric oxygen has been recommended as a useful adjunct for treating diabetic foot ulcers
- a literature review was completed to evaluate the prospective and retrospective studies completed on hyperbaric oxygen for diabetic foot ulcers

HBO could enhance the effect of antibiotics, which could reduce the development of infection and its subsequent effects. Infection in DFUs can spread rapidly and lead to hospitalisation, impaired healing and amputation(21). HBO has also been observed to reduce pathological inflammation by lessening neutrophil adhesion and reducing apoptosis(22,23) and thus has the potential to facilitate healing in DFUs that have become stalled in the inflammatory phase of healing.

A literature review was completed to evaluate the clinical evidence available on HBO for DFUs.

Methods

Literature searches were conducted using Pubmed and Cinahl using the search terms, 'hyperbaric', 'diabetic', 'foot ulcers', 'retrospective' and 'systematic review' in various combinations to find relevant clinical trials and systematic reviews. The systematic reviews were then studied for other pertinent references.

Prospective and retrospective studies were found and their methods and findings were reviewed and evaluated.

Table 1 Results from literature search

Authors	Year of publication	Country of study
Prospective studies		
Baroni *et al.* (25)	1987	Italy
Oriani *et al.* (26)	1990	Italy
Doctor *et al.* (27)	1992	India
Faglia *et al.* (28,29)	1996	Italy
Zamboni *et al.* (30)	1997	USA
Kalani *et al.* (31)	2002	Sweden
Abidia *et al.* (24)	2003	UK
Kessler *et al.* (32)	2003	France
Duzgun *et al.* (33)	2008	Turkey
Löndahl *et al.* (12,34,35)	2010	Sweden
Retrospective studies		
Cianci & Hunt (36)	1997	USA
Faglia *et al.* (28,29)	1998	Italy
Zgonis *et al.* (37)	2005	USA
Fife *et al.* (38)	2007	USA
Oubre *et al.* (39)	2007	USA
Ong (40)	2008	Singapore
Lyon (41)	2008	USA

Results

The searches resulted in ten prospective and seven retrospective clinical studies on the use of HBO for the treatment of DFUs being considered applicable to this review and written in English. Of the ten prospective studies found, only five were published in the last 10 years with the earliest published in 1987. A number of developments and improvements have been made to health care systems during the 22 years over which all these studies were performed and only one study(24) was undertaken in the UK. Most of the prospective studies also had relatively small treatment groups. All the retrospective studies were completed within the last 14 years making them far more relevant to current clinical practice. Table 1 lists the publications identified.

Discussion

Prospective studies

Baroni *et al*. (25) observed improved wound healing and reduced amputation rate in patients who received HBO ($n = 18$) compared with patients who received conventional treatment alone ($n = 10$). These results were found to be statistically significant ($P = 0{\cdot}001$) but they may not be clinically significant as the small sample size may not be representative of the population. All patients had retinopathy and there were more type 1 diabetics in the HBO group. Oriani *et al*. (26) conducted a similar study and found a significant difference in amputation rate, with HBO-treated patients ($n = 62$) having an improved outcome compared with those unsuitable for HBO because of treatment contraindications ($n = 18$). Both studies optimised metabolic control, provided debridement of the wounds and administered antibiotics as indicated by bacterial tests. Although there was a similar distribution of major diabetic complications between the groups, the large difference in numbers requires some caution to be taken when comparing their outcomes. In both studies, HBO patients were treated at either 2·8 atmospheres absolute (ATA; for antibacterial support) or 2·5 ATA (for reparative effect) and both were unrandomised and unblinded. Baroni *et al*. (25) support their choice of regime with reference to work on rabbits by Hunt and Pai (42) and Hunt *et al*. (43). The latter experiments observed lower concentrations of bacteria and less infection in rabbits exposed to higher oxygen tensions. These treatment protocols are not currently routine in British hyperbaric centres and are not advised in the current Undersea and Hyperbaric Medial Society (UHMS) guidelines(44). Baroni *et al*. (25) administered $34 \pm 21{\cdot}8$ daily treatments, while Oriani *et al*. (26) treated patients for 6 days/week at 2·8 ATA until granulation began and then 5 days/week at 2·5 ATA until recovery (not defined). These patients received on average 72 ± 29 HBO sessions. This is a higher number of treatments than is routinely administered in the UK where 30–40 treatments are reported as common(11). However, the UHMS do not recommend a specific number of treatments in their guidance, just a review after the initial 30 days of HBO and at least every 30 days thereafter(44).

Doctor *et al*. (27) undertook a prospective study on 30 hospitalised diabetic patients with chronic (not defined) foot lesions to evaluate the adjunctive effect of HBO on DFUs. Outcome measures included daily wound assessment, length of hospital stay, need for and level of amputation and wound cultures taken before and after each HBO session. The authors have not specified the causes of the lesions. The study was unblinded and the method of randomisation was not specified, therefore bias may have influenced reported outcomes. Patients were randomised to receive either conventional treatment alone or HBO as an adjunct. Their report does not clarify how many patients were allocated to each group, although they do show that groups were closely matched for age and sex. Some aspects of care were standardised, including wound

care and insulin treatment to maintain good diabetic control, thus reducing the influence of confounding factors. Debridement formed part of their wound care regime and antibiotics were administered as required. All HBO patients received four treatments at three atmospheres for 45 minutes over a 2-week period, which is a highly unusual treatment regime. Doctor *et al*. (27) reported the length of hospital stay, while shorter for the HBO group, was not statistically significant but, like Oriani *et al*. (26) and Baroni *et al*. (25), they did observe a significant reduction in major amputation rate (defined as amputation above the ankle joint) compared with the control group. They also suggested that HBO controlled wound infection, specifically *Pseudomonas* and *Escherichia coli* as there were a reduced number of positive wound cultures following HBO treatment. Unfortunately, wound healing data were not reported. Because of the overall poor reporting of this study, results must be interpreted with caution.

Faglia *et al*. (28) also focussed on evaluating the effect of HBO on major amputation rate in patients hospitalised for DFUs and also observed a statistically significant reduction in major amputations in the group treated with HBO compared with the control group. Metabolic control was optimised and antibiotics were provided for all patients. Thirty-five patients were randomised to the HBO group and 33 to the control group ($n = 68$). Unlike Doctor *et al*. (27), Faglia *et al*. (28) used Wagner grading(45) to assess ulcer severity and grades 2–4 ulcers were included in the study. The surgeon assessing the need for amputation was blinded to the treatment group, so increasing the reliability of the study. As in the study by Oriani *et al*. (26), treatment was in two phases – initially, daily HBO at 2·5 ATA for 90 minutes was administered, with a second phase at 2·4–2·2 ATA for 90 minutes, 5 days a week. The first phase of treatment was intended to enhance the antibacterial effect and to rapidly restore sufficient tissue oxygen tension, while the second phase was to stimulate fibroblast activity. Faglia *et al*. (28) discuss some in vitro and animal studies to support their treatment depths(46–48), although none actually used the combined regime provided in this trial. Patients received an average of 38 ± 8 treatments, although information on the distribution of these treatments between the two phases is lacking. Results show a statistically significant reduction in major amputation for patients treated with HBO. As Wagner grade 4 ulcers were the most common in this study population, Faglia *et al*. (28) concluded that adjunctive HBO is effective in decreasing major amputation in patients with severe DFUs.

A smaller study by Zamboni *et al*. (30) ($n = 10$) compared the healing rate of DFUs in five patients who received HBO with five control patients. Patients were selected consecutively and patients who refused HBO formed the control group. This selection method is common in HBO studies, often being considered ethically more acceptable than other methods. However, those that consented to receive HBO may have been more motivated towards positive health behaviour than those that refused causing selection bias and reducing the validity of the study(49). In non-randomised group allocation such as this, the patients' motivations for refusing the experimental treatment should be considered(50). In this study, two patients refused HBO due to claustrophobia – a recognised side effect of HBO(44) – and three patients refused due to living in rural locations. Both groups received standardised care including debridement, weekly wound surface area measurements by an individual blinded to group allocation, and outcomes were compared at week 7, following completion of 30 treatments at 2·0 ATA once a day, 5 days a week. Wound care was provided twice daily to all patients by a home nurse or hyperbaric technician and the same dressing types were used for both groups. Such a high frequency of dressing changes is not common in routine treatment of DFUs in the UK. Endpoints were complete wound healing or amputation. A significantly greater reduction in wound surface area was observed in the HBO group compared with that of the control group. Unlike the previous studies, follow-up continued for 4–6 months after which ulcers remained present in 80% of patients from the control group, while 80% of patients in the HBO group had healed (not defined) with the fifth patient undergoing surgical coverage. These results suggest that HBO improves DFU healing, although due to the small sample size and lack of information on ulcer severity, these results cannot be generalised.

Thirty-eight patients with chronic DFUs and local hypoxia [defined as ulcer duration >2 months and transcutaneous oxygen monitoring ($TcPO_2$) <40 mmHg] were investigated and followed-up for 3 years by Kalani *et al*. (31) to study the long-term effect of HBO. All patients were under the management of the foot ulcer team and were provided with orthotic footwear/devices and their metabolic control, blood pressure and nutrition were optimised. Antibiotics were administered as required. Patients were considered for inclusion in this study if their ulcers remained unhealed despite this treatment regime. Randomisation was attempted initially but, because of restricted local availability of HBO, allocation to the treatment or control group was determined on the basis of local access. Seventeen patients received adjunctive HBO and 21 were treated with standard care alone. Wound surface area and ulcer depth were monitored with no blinding during assessment reported. At 3-year follow-up, 13 of the HBO group had healed (intact skin) and 2 patients had undergone below knee amputations (the remaining 2 died), while 10 of the control group healed and 7 underwent below knee amputation (3 patients died and 1 showed improved ulcer healing). Time for healing was similar in both groups. The patients in the HBO group were younger and so may have had better healing potential, however, the HBO group also consisted of more type 1 diabetics and they had a greater ulcer area initially. Kalani *et al*. (31) concluded that these results suggest an accelerated healing rate and reduced need for amputation, supporting the results of previous trials. However, this trial, like others, had small patient numbers when compared with the DFU population as a whole.

A double-blind trial by Abidia *et al*. (24) investigated the therapeutic effect of HBO on DFUs in the presence of peripheral arterial disease and observed improved healing in those patients treated with HBO. Patients for whom vascular surgical procedures were planned were excluded leaving 18 suitable patients whose wounds had been present for over 6 weeks to be randomised to receive either HBO or sham treatments. Only the chamber operator knew to which group each of the patients belonged. Two patients withdrew from

the study, one from each group, leaving eight patients in each arm. All patients received offloading and debridement of their ulcers and antibiotics were prescribed when there were clinical signs of infection. Patients received five treatments per week for 6 weeks at 2·4 ATA with HBO patients inhaling 100% oxygen for 90 minutes and the control patients inhaling air. Results showed healing (defined as complete epithelialisation) in five of eight patients in the HBO group but in only one from the control group after 6 weeks. Wound surface area and depth were monitored. At 6 month follow-up, the median decrease in wound area was similar for both groups – 100% for the HBO group and 95% for the control group. At 1 year, five patients remained healed in the HBO group, whereas none of the control group was healed, suggesting HBO has a prolonged effect. Abidia *et al*. (24) also evaluated the influence of HBO on quality of life (QoL) using the short form 36 (SF-36) and the Hospital Anxiety and Depression Scale and found no significant improvements in QoL compared with the control group. QoL can have a substantial effect on wound healing. Not only can poor QoL lead to reduced compliance with treatment, but evidence suggests that stress and lack of social support can have negative effects on the wound healing process(51–53). A limited evaluation of the economic impact of HBO for these patients suggested an average saving of £2960 per patient in the follow-up year because of the reduced number of dressing visits required compared with those patients who did not have HBO. Kranke *et al*. (54) propose that this analysis is unreliable, as the methodology is not reported in detail and Abidia *et al*. (24) highlight that this calculation is neither accurate nor consistent with other units because of the varying costs of treatment.

Kessler *et al*. (32) reported a study to determine the effect of HBO on healing rate in patients with DFUs Wagner grades 1–3 whose ulcers had been present for at least 3 months and showed no improvement with conventional treatment despite ulcer offloading and stabilisation of glycaemic control. Twenty-eight patients were randomised to receive either standard treatment plus HBO ($n = 15$) or standard treatment alone ($n = 13$) and the main outcome measure was ulcer size, calculated using tracings. Patients in the treatment arm received HBO at 2·5 ATA for 90 minutes twice a day, 5 days a week for 2 weeks and follow-up continued for 2 weeks. Results showed a statistically significant greater percentage reduction in ulcer size for the HBO group after 2 weeks of treatment (41·8 ± 25·5% compared with 21·7 ± 16·9% for the control group) but 2 weeks later reduction in ulcer size was comparable between the groups (48·1 ± 30·3% for the HBO group and 41·7 ± 27·3% for the control group). After 4 weeks, healing was observed in two patients who received HBO but in none who received standard treatment alone. The authors concluded that HBO doubled the mean healing rate of DFUs, however, their follow-up results suggested that this increase in healing may only be short term. This is the only trial where patients were treated with HBO twice daily – this could be a factor that influenced their outcomes and explain why results differed from other studies. The UHMS recommended treatment is administered on a once daily basis unless the wound is severely infected when twice daily HBO may be more appropriate(44). Kessler *et al*. (32) state that no patients in this trial showed any signs of clinical infection.

Duzgun *et al*. (33) investigated the effect of HBO on infected DFUs that had been present for at least 4 weeks. Although ulcers were graded using the Wagner classification system, Duzgun *et al*. (33) did not distinguish between ischaemic and neuropathic ulcers. Patients were randomised to receive either adjunctive HBO at 2–3 ATA for 90 minutes or standard care alone. All patients received daily wound care, debridement and antibiotics as required. The hyperbaric treatment regime involved twice daily alternated with once daily treatments for 20–30 days. This is an unusual treatment regime and no justification was provided for its use. The mean follow-up duration was 92 ± 12 weeks. Fifty patients were allocated to each group with a statistically significant higher proportion of males, obese patients and smokers in the HBO group – the authors have suggested this difference between groups occurred by chance as they were unable to find any other explanation. Six outcome measures were used – total closure of the wound with no surgical intervention required, graft or flap required, amputation distal to the metatarsophalangeal joints required, amputation proximal to the metatarsophalangeal joints required, no change (defined as no sign of healing during the course of treatment) and operative surgical debridement required to achieve complete wound closure. As with the previous studies, patients treated with HBO experienced better overall results than the standard group – 33 HBO patients healed without any surgical intervention compared with none in the control group and only 4 HBO patients received amputations compared with 41 in the standard treatment group. This was despite the higher level of wound healing risk factors in the HBO group.

Löndahl *et al*. (34) recently published results of a double-blind randomised placebo controlled trial and concluded that HBO doubled the number of healed ulcers at 1-year follow-up period compared with placebo. A total of 94 patients with wounds below the malleolus that had been present for at least 3 months (range = 3–44 months) were randomised to receive either HBO ($n = 49$) or placebo ($n = 45$). All patients were treated at 2·5 ATA and, as in the study by Abidia *et al*. (24), were given either air or 100% oxygen for 90 minutes. Treatment was given once daily Monday to Friday with weekends off for a total of 8 weeks. Treatment was extended for up to 2 weeks when patients had missed therapy, but the maximum number of treatments administered was 40. There were withdrawals from both the study and control groups with a total of 38 HBO and 37 placebo patients completing more than 35 treatment sessions. Treatment was administered as an adjunct to routine care provided by the multidisciplinary clinic and the HBO and control groups were similarly matched demographically. However, while not significant, there were more current smokers in the control group and more type 2 diabetics in the HBO group. The primary endpoint of complete healing was achieved in 37 patients at 1-year follow-up period – 52% of HBO group and 29% of the placebo group ($P = 0·03$). Of those participants completing more than 35 sessions, 61% of the HBO group and 27% of the control group healed ($P = 0·009$). The largest difference in healing rate was reported to be seen at 9-month follow-up highlighting the

continued benefit after the course of HBO has been completed. Löndahl *et al*. (34) calculated that the number needed to treat to avert non-healing of a chronic foot ulcer is 4·2 according to the intention to treat analysis and 3·1 for the per-protocol analysis. In a separate publication, Löndahl *et al*. (35) reported that the QoL of patients in this study was assessed using the SF-36 and improved QoL was observed at 1-year follow-up.

Retrospective Studies

Retrospective reviews are often conducted in areas where treatments are already routinely used and they allow the researcher to investigate outcomes from existing data and observe relationships between patient characteristics and treatment outcomes. Such research lacks the control that can be applied in prospective studies and relies on the quality of existing data and documentation, which may be incomplete and inconsistent(55). However, they enable patients representative of the population to be investigated without the strict inclusion criteria used in many prospective trials and can result in larger patient numbers.

A retrospective study by Cianci and Hunt (36) examined long-term outcomes in patients treated with vascular surgery and adjunctive HBO to determine whether such an approach could be cost-effective. They reviewed the records of 41 patients with chronic Wagner grade 3 or 4 DFUs. 'Initial salvage' (complete wound closure, preservation of the foot or restoration of ambulation) had been achieved in 35 of these patients (85%). The patient sample was small, with the 41 patients treated over a 7-year period (1983–1990). All patients were at risk of losing a limb. In 1991, the wounds of 27 patients remained intact with a mean durability of repair of 32 months (one patient underwent a below knee amputation). The remaining 14 were lost to follow-up. In 1993, 22 of those 27 patients still had healed wounds. The long-term outcome for this small group of patients was good and the authors suggest such a treatment regime could be cost-effective, but the size of the review does not allow these results to be generalised to the entire DFU population.

In 1998, Faglia *et al*. (29) reviewed patient outcome in order to compare amputation rates between 1990 and 1993 with results observed in two previous prospective studies(25,28). Of 115 patients treated, 51 were given HBO using the same regime as discussed for the two earlier studies. Patients received a mean number of 32 $\pm$ 11 HBO treatments with only 7 of these patients receiving major amputations compared with 20 patients in the group who did not receive HBO ($P = 0{\cdot}012$). The clinical characteristics were found to be similar in each group apart from age, which was higher in the non-HBO group. Being retrospective, caution should be taken before drawing any conclusions from this study alone, although it does support findings from the prospective studies discussed above.

A retrospective study assessing the relationship between HBO and patient outcome following partial foot amputation(37) found that 70% of patients (35 patients with 40 wounds) experienced healing or no further surgical procedures required to heal the site after HBO. Patients with a successful outcome had a mean number of 20 HBO treatments and took a mean of 44 days to reach that point compared with the failed group who received a mean of 16 HBO treatments and took 216 days to final outcome. Zgonis *et al*. (37) explained that conclusions cannot be drawn from this study and intend that it is used as a starting point on which future research is based. The retrospective nature of the study did not allow for a control group with which to compare outcomes and the patient numbers are small considering the fact that data over a 10-year period was reviewed. These drawbacks do suggest the study results are unreliable and while the methods can be used to aid planning of future studies, patient outcomes cannot be applied more generally.

The largest retrospective study investigating outcomes for 971 patients who received HBO for diabetic lower extremity ulcers found that 717 (73·8%) of patients improved with a mean of 34 HBO treatments(38). Those patients who did not improve received a mean number of 24 therapies. Fife *et al*. (38) suggest that the discontinuation of treatment that appeared to be ineffective generally occurred at this point. This multi-institutional study is the largest published in terms of sample size and information retrieved. Fife *et al*. (38) attempted to reduce the inconsistencies that can occur in retrospective studies by allowing the retrospective data retrieval to be undertaken by one observer. The origin of each of the three largest wounds per patient was allocated to one of the following groups; spontaneous or not known, post operative or trauma. Fife *et al*. (38) highlighted that the main objective of HBO may be partial healing and stimulation of granulation allowing healing and epithelialisation to continue after the completion of HBO. This objective is not always taken into consideration when the outcome of treatment is evaluated and yet these are often chronic wounds that have not shown any improvement for a number of weeks or months and amputation may be the only alternative option. Results showed that only 79 of 136 patients (58%) with renal failure improved compared with 638 of 835 (76%) without renal failure. Because of the large difference in outcome for patients with and without renal failure, Fife *et al*. (38) removed the renal failure patients from the statistical analyses of the variables to avoid confounding the results. There was no statistically significant difference found, neither between insulin and non-insulin diabetics nor in neuropathy status, although the 'insensate' category experienced twice the amputation rate of the 'normal' and 'decreased sensation' categories. Patients who received one HBO treatment a day had more positive outcomes than those who were treated twice daily, although Fife *et al*. (38) suggest that this may be due to patients with more compromised limbs being treated more intensively rather than the higher frequency of treatment being less effective. Patients who achieved higher increases in their $TcPO_2$while breathing 100% oxygen at depth experienced better outcomes. No significant difference was found in outcome between patients who had a prior amputation and those who had not. Those patients who had a >40 pack-year history of smoking had a significantly worse outcome than those with <40 pack-years or those who had never smoked. Otto *et al*. (56) published a paper investigating the effects of smoking on outcome of HBO and found statistically significant evidence that smoking is a risk factor for the

healing of wounds in diabetic patients undergoing HBO. This was a larger study than Faglia *et al*. (29) where no significant link was found between smoking and outcome of HBO. Patients with renal failure, two or more ulcers and a Wagner grade 3 or above were found to have a poor overall outcome following HBO treatment. Only 3-week follow-up was achieved on this sample, so the long-term outcomes have not been reported.

A study scrutinising patient records from a 6-year period compared the outcomes of patients affected by different health factors following HBO for lower extremity wounds(39). They intended to identify which health factors affected wound healing. Treatment was administered daily at 2·4 ATA for 6 weeks and diabetics ($n = 37$) were not found to have a significant difference in wound area reduction to that seen in non-diabetics ($n = 37$), although a breakdown of how many diabetic patients achieved the outcomes of 'robust healing' (over 50% reduction in wound area), 'minimal healing' (15% reduction) and 'non-healing' (60% increase in area) was not provided. These outcome groups varied greatly and there was no explanation for how patients were allocated to a group if their wounds fell outside these parameters. Seventy-three patients with 85 non-healing lower extremity ulcers were included in the analysis and Oubre *et al*. (39) found that although diabetes was not associated with a poor outcome, smoking did result in a poorer outcome ($P < 0{\cdot}0001$) and patients who fared better had higher $TcPO_2$ results and were younger.

Ong(40) examined DFUs over a 10-month period and observed that 71% of patients had a favourable outcome of ≥80% granulating tissue or partial or complete epithelialisation following a course of HBO. The mean number of treatments was 20 at 2·5 ATA once daily with weekends off. Of the 45 wounds described as foot ulcers, 2 were non-healing below knee amputation wounds and a small number (not specified) were leg ulcers; therefore, the inclusion of these patients could have skewed the results.

A retrospective analysis of healing rates for patients admitted to a wound centre over an 8-week period reported that patients receiving HBO ($n = 38$) showed statistically significantly better healing ($P < 0{\cdot}0001$) than those who received standard wound care or growth factor therapy alone(41). Unfortunately, Lyon(41) did not show the number of HBO treatments received nor the treatment depth and regime. The 89 patients all had lower extremity ulcers, the aetiology of which are not defined, but pictures of wounds to legs are included. No disclosure of the location of the wounds is provided, so the percentage of foot ulcers is unknown.

Conclusion

The results of all these studies (prospective and retrospective) support the suggestion that HBO improves healing in patients with DFUs and can lead to a reduction in major amputation. Only a few of the studies investigated long-term outcomes, but these suggested that wounds that healed by HBO were likely to remain intact in the future. As well as affecting a patient's QoL, DFUs have a significant impact on society, financially and socially, therefore interventions that can help reduce ulcer recurrence and amputation rates should be considered.

Most studies had methodological flaws and small sample size and although results are promising more robust research is required before substantial conclusions can be made. Further research with larger numbers of participants would be advantageous to investigate the effect of different variables on patient outcome in the short and long term, particularly $TcPO_2$, smoking, age, renal failure and ulcer severity. Findings from such studies would allow clinicians to make more informed choices regarding which patients are most likely to benefit from a course of HBO.

Although blinded randomised controlled trials (RCTs) are the gold standard of evidence, they are not straightforward to design or conduct and may provide ethical dilemmas in areas where the gold standard treatment is already offered. Clinicians already using HBO as a part of their treatment pathway for patients with DFUs might be reluctant to encourage patients to participate in a study where they may be randomised not to receive HBO. However, an RCT investigating long-term follow-up and health economics as well as patient's QoL would enable the true value of HBO to be more accurately assessed.

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